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URINARY ESTROGENS (MEASURED FLUOROMETRICALLY AND BIOLOGICALLY) IN HYPERADRENOCORTICISM: INFLUENCE OF CORTISONE, COMPOUND F, COMPOUND B AND ACTH*

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WHEREAS the role of the adrenal cortex in promoting urinary excretion of 17-ketosteroids and reducing corticoids in man has been established, the participation of the adrenals in the production of urinary estrogens has not been well investigated. That the adrenal glands are involved in estrogen metabolism is indicated by the fact that estrone has been extracted from ox adrenal glands (1). Adrenocortical tumors causing either virilization, Cushing's syndrome or feminization with gynecomastia, sometimes produce an increased excretion of estrogens, but this is not always so. In congenital adrenal hyperplasia, there is usually an increase of the urinary excretion of fluorometrically measured estrogens (2).

It has recently been shown that cortisone therapy reduces the urinary 17-ketosteroid excretion to a normal level in patients with congenital adrenal hyperplasia (2–5), but usually does not decrease the 17-ketosteroid

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† Fellow of the André and Bella Meyer Foundation (France) on the recommendation of the Institute of International Education, New York.

output in cases of adrenal tumor (6, 7). It has been suggested that this response of 17-ketosteroids to cortisone therapy may be used as a test to differentiate congenital adrenal hyperplasia from adrenal tumors with elevated 17-ketosteroid excretion (7).

The present observations represent a study of some aspects of estrogen metabolism in hyperadrenocorticism. The urinary estrogens were determined chemically and in a few cases biologically. The changes in their excretion under cortisone therapy were followed. These studies were made in 3 cases of adrenal tumor of the virilizing or hirsutizing type, in 13 cases of congenital adrenal hyperplasia (10 female pseudohermaphrodites and 3 males with macrogenitosomia precox), in 1 case of acquired adrenal hyperplasia and in 4 cases of Cushing's syndrome (1 due to a malignant adrenal tumor). In order to provide control data, the estrogen excretion of a normal adult male was measured during a control period and during cortisone therapy.

METHODS

All studies were made on 24-hour urine collections which were preserved with 15 ml. of 25 per cent acetic acid. The specimens were usually refrigerated during collection. The following determinations were made: chemical assay of estrogens by fluorometry, biologic assay of estrogens in some instances, and chemical assay of 17-ketosteroids, dehydroisoandrosterone and reducing corticoids (11-oxysteroids).

1. *The chemical determination of urinary estrogens* (fluorogenic phenols) was performed by a slight modification of Jailer's method (8). To 100 ml. of the 24-hour urine collection was added 10 ml. of concentrated HCl. This was boiled for fifteen minutes. The hydrolyzed urine was then cooled and saturated with NaCl. The urine was extracted three times, using 35 ml. of Merck benzene each time. The benzene extract was washed twice with 25 ml. of 9 per cent $NaHCO_3$ and once with 25 ml. of distilled water. The estrogens were extracted from the benzene by 25 ml. of normal NaOH; this procedure was repeated four times. The NaOH solution was acidified with 25 ml. of concentrated HCl, cooled and extracted three times with 35 ml. of benzene. The benzene extract was washed with 25 ml. of $NaHCO_3$ and 25 ml. of water and evaporated to dryness under vacuum. The residue was dissolved in 2 ml. of redistilled absolute ethyl alcohol. Two-tenths ml. of the alcoholic extract was added to 1 ml. of concentrated H_2SO_4 and put in a boiling water bath for twenty minutes, after which 6 ml. of 65 per cent H_2SO_4 was added. The fluorescence of the specimen was read with a Coleman electronic photofluorometer, model 12A, using filter PC-9A and filters B-1 and B-2 as described by Jailer (8). The sensitivity of the instrument was calibrated with quinine sulfate solution (0.3 mg. per liter in N/10 sulfuric acid). The fluoresence was compared with that of a standard solution of α-estradiol in redistilled absolute ethyl alcohol (0.1 mg. per 100 ml.). A blank was used which had been prepared with the reagents. The recovery of a standard solution of α-estradiol was run in each set of determinations. New reagents were checked before use, because occasionally sulfuric acid was found to contain substances which inhibited fluorescence. Certain brands of benzene (Baker, Will Corp. 99 per cent) were found to

contain a large amount of fluorescent substances. Benzene Merck (thiophene free) was found to be satisfactory, but at times exhibited extra fluorescence.

2. *Biologic assay of urinary estrogens.*[1] The urinary extracts were made from a 24-hour urine collection, or from aliquots of the pooled specimens of two or more days. The estrogen extractions for bioassay were made in a similar manner to the extraction just described for the chemical determinations, but the quantity of reagents was adjusted to the volume of each specimen. At the end of the extraction, the benzene was evaporated to dryness. The residue was dissolved in ether and added to 3 ml. of sesame oil. Assays were made by the method of Evans, Varney and Koch (9). The ether was evaporated and three different dilutions (1:4, 1:16, 1:64) of estrogen residue were made from each urine specimen. Each of the three levels plus an undiluted aliquot was tested on a group of 5 immature female mice (21 days old): 0.05 ml. of the oil solution was injected subcutaneously into each mouse, twice a day for three days (*i.e.*, a total of 0.3 ml. of sesame oil per mouse). The mice were sacrificed on the fourth day. Each uterus with its tubes was dissected out carefully and weighed on a Roller-Smith torsion balance. Ten control mice received treatment with a pure solution of sesame oil. Five different standard solutions of α-estradiol in sesame oil were made so that they contained respectively 0.1, 0.075, 0.050, 0.025 and 0.010 microgram of α-estradiol per 0.3 ml. of oil. Each standard solution was tested on a group of 5 mice in the same way as for the unknown solutions. The average increase of uterus weight over the control was calculated. Values found for standard solutions were used for the construction of a calibration curve. The biologically

TABLE 1. EFFECT OF CORTISONE AND ACTH ON URINARY ESTROGENS IN ADRENOCORTICAL TUMORS

Case	Sex	Age (yrs.)	Clinical type	Treatment	Days of study*	Urinary estrogens (γ/av. per 24 hrs. as α-estradiol)		Urinary 17-KS, (mg./av. per 24 hrs.)
						Fluorometric	Biologic	
1/E.H.	F	35	Hirsutizing; no metastases	None	1–10	84.5	14	73.7
				Cortisone, 100 mg. (oral)	11–16	111.1	12	123.6
				None	17–21	90.0		125.0
				After tumor removal	23–30	38.5	1.1	7.4
2/H.B.	M	4¾	Virilizing; no metastases	None	1–3	79.6		194.0
				ACTH, 50 mg. i.v.	4	101.0		231.0
				None (after aortogram)	8–20	283.0	16.0	378.0
				Cortisone, 100 mg. (oral)	21–28	524.0	48.0	409.0
				None	29–33	363.5		265.6
				After tumor removal	35–42	33.5	0.4	2.9
3/M.B.	F	3	Virilizing; no metastases	None	1–6	45.8		41.0
				ACTH, 50 mg. i.v.	7	47.5		50.0
				None	8–10	32.5		40.4
				Cortisone, 100 mg.(oral)	11–15	51.5		64.8
				None	16–23	45.0		62.0
				After tumor removal	25–33	14.0		0.9

* "Days of study" are numbered from the day when the investigation were begun. The values for estrogens and 17-KS are the average of all the determinations made during the periods indicated.

[1] The authors are indebted to Dr. W. W. Scott for valuable assistance in standardizing this technique.

determined estrogens were expressed as weight in micrograms of α-estradiol with an equivalent activity. The results have to be multiplied by 10 to convert them to International Units.

3. *Other urinary steroids.* The methods used for the determination of other steroids were: 17-ketosteroids by the method of Callow and colleagues (10), dehydroisoandrosterone-like steroids by the method of Allen and colleagues (11) and reducing corticoids by the phosphomolybdic acid reduction reaction (12, 13).

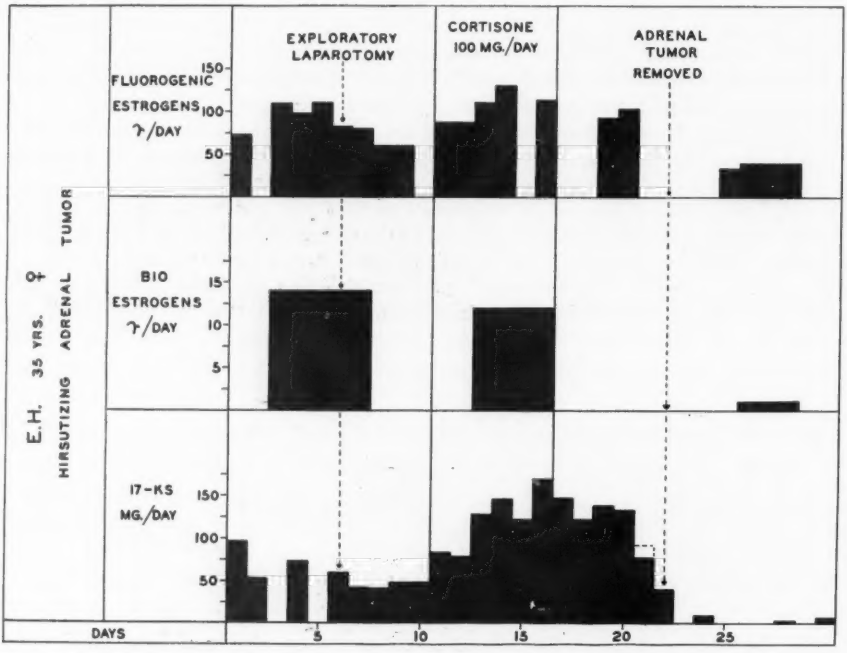

FIG. 1. Urinary steroids in Case 1 (adrenal tumor). The slightly increased urinary estrogens were not changed by cortisone administration.

RESULTS

1. *Adrenocortical tumors of the virilizing type*

One adult and 2 children with tumors causing virilization or hirsutism were studied. None of these tumors had metastasized and in each case a well encapsulated neoplasm was removed surgically. Additional data on these cases have been reported elsewhere (14). In Table 1 the average daily urinary excretions of fluorometrically measured estrogens and 17-ketosteroids are compared during a control period, during cortisone administration and after removal of the tumor. In 2 of the patients, measurements were made on the day during which continuous infusions of ACTH

were given for twelve hours. In 2 patients estrogens were determined biologically.

During the control period, the fluorometrically measured estrogens were 84.5, 79.6 and 45.8 micrograms per day and the urinary 17-ketosteroids were 73.7, 194 and 41 mg. per twenty-four hours, respectively. The oral administration of cortisone did not reduce the output of either estrogens

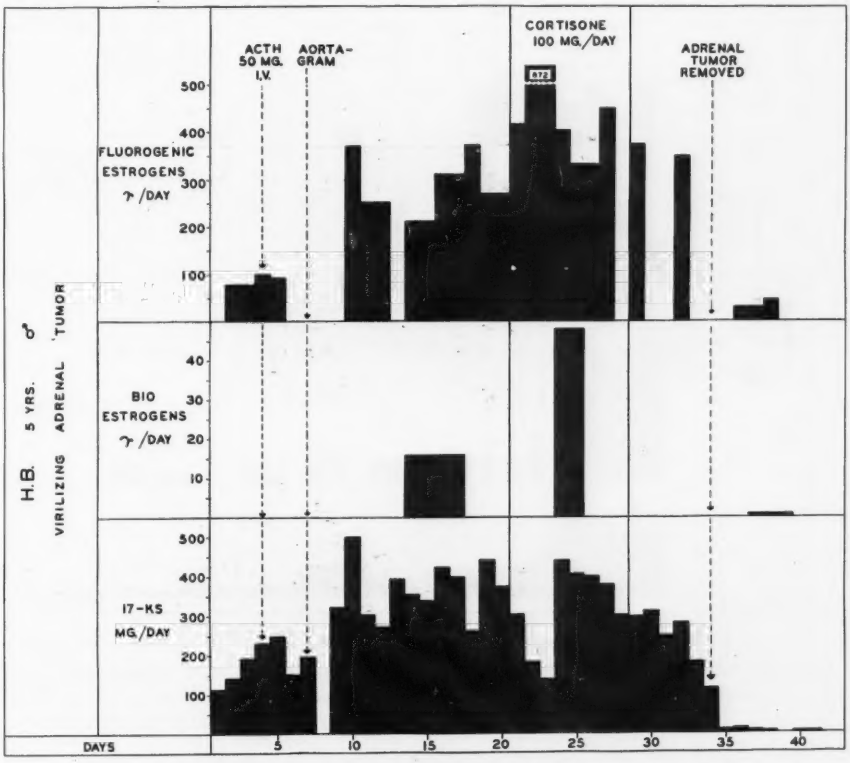

FIG. 2. Urinary steroids in Case 2 (adrenal tumor).

or 17-ketosteroids; in fact there was a slight increase of estrogens in Cases 1 and 3, and a great increase in Case 2 (Figs. 1, 2 and 3). In Cases 1 and 3 the urinary 17-ketosteroids increased simultaneously. In Case 2 at the beginning of cortisone administration, a sharp decrease of the 17-ketosteroids corresponded to a large increase of fluorometrically measured estrogens. On the following days of cortisone administration, the fluorometrically measured estrogens went to a lower but still high level when the urinary 17-ketosteroids increased (Fig. 2). The changes in steroid excretion are

difficult to interpret. The administration of intravenous ACTH caused only very slight changes in either estrogens or 17-ketosteroids (Cases 2 and 3). In Patient H. B. (Case 2) an aortogram was made following catheterization of the femoral artery, in an attempt to visualize the tumor. On the days following this procedure there was a marked increase in both estrogens and 17-ketosteroids. After removal of the tumors in the 3 pa-

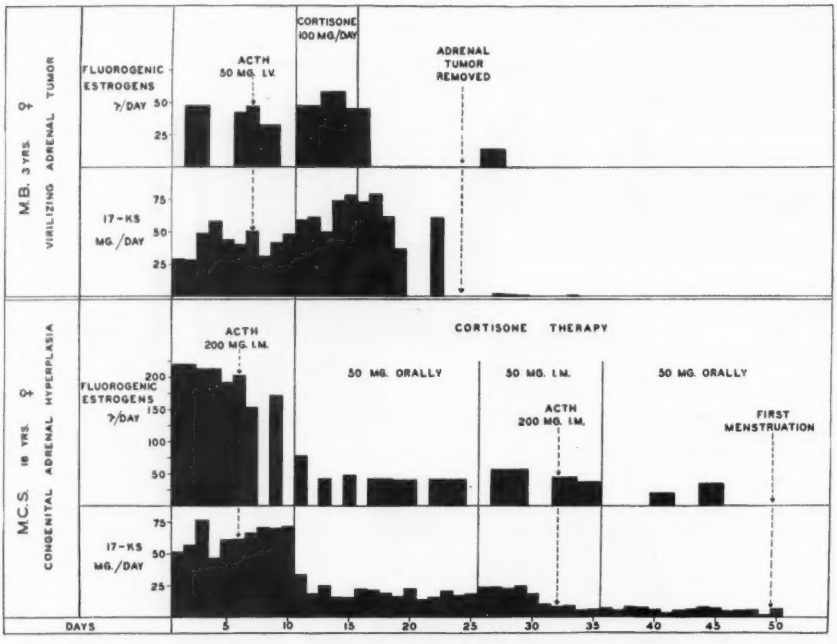

FIG. 3. Effect of cortisone administration on urinary steroid excretion in a patient with adrenal tumor (Case 3) and in a patient with congenital adrenal hyperplasia (Case 6). Whereas fluorogenic estrogens and 17-ketosteroids were unchanged or possibly increased in the case of adrenal tumor, they were sharply decreased in the case of congenital adrenal hyperplasia.

tients, the urinary excretions of fluorometrically measured estrogens were respectively 38.5, 33.5 and 14 micrograms per twenty-four hours, and the urinary 17-ketosteroids 7.4, 2.9 and 0.9 mg. per twenty-four hours.

Urinary estrogens were measured biologically in Cases 1 and 2. During the control period, estrogenic activities equivalent to those of 14 and 16 micrograms of α-estradiol were found. During cortisone administration, there was a marked increase in the biologically measured estrogens of Case 2, but no change in Case 1. Following removal of the tumors, the values fell to 1.1 and 0.4 micrograms per twenty-four hours.

TABLE 2. EFFECT OF CORTISONE, ACTH AND COMPOUND F ON URINARY ESTROGENS IN CONGENITAL ADRENAL HYPERPLASIA

(Female pseudohermaphrodites over 6 years of age)

Case	Sex	Age (yrs.)	Treatment			Days of study*	Urinary fluorogenic estrogens (γ/av. per 24 hrs. as α-estradiol)	Urinary 17-KS (mg./av. per 24 hrs.)
			Cortisone	ACTH	Other			
4/D.P.	F	49	0	0	Insulin	Control	158.0	68.0
			100 mg. i.m.	0	Insulin	5–7	32.0	3.5
5/J.S.	F	18½	0	0		Control	93.0	53.2
			50 mg. i.m.	0		10–20	40.0	4.1
			25 mg.i.m.	0		18–121	39.0	5.3
6/M.C.S.	F	16¼	0	0		1–5	212.4	59.1
			0	200 mg. i.m.		6	204.0	62.6
			50 mg. (oral)	0		11–25	41.9	19.9
			50 mg. i.m.	0		26–31	57.0	21.0
			50 mg. i.m.	200 mg. i.m.		32	45.0	9.0
			50 mg. (oral)	0		36–50	27.7	6.2
7/P.R.	F	16	0	0		Control	111.5	45.0
			0	200 mg. i.m.		Control	112.0	50.5
			100 mg. (oral)	0		1–13	37.5	7.0
			100 mg. (oral)	200 mg. i.m.		14	48.0	7.3
			25 mg. (oral)	0		17–22	72.5	22.0
			50 mg. (oral)	0		23–31	34.5	9.0
8/M.N.	F	10½	0	0		Control	73.0	40.0
			0	0	Cpd. F, 25 mg. i.m.	1–21	38.0	12.5
			50 mg. (oral)	0		22–40	33.5	4.7
			50 mg. (oral)	50 mg. i.v.		224	52.5	6.9
			50 mg. (oral)	100 mg. i.m.		229–231	96.5	10.9
			0	0		236–243	105.0	11.1
			0	100 mg. i.m.		244–247	103.0	11.5
9/W.D.	F	9	0	0		Control	65.0	39.2
			0	50 mg. i.v.		Control	104.0	68.7
			25 mg. (oral)	0		11	28.5	20.0
			50 mg. (oral)	0		64	18.0	3.2
10/T.T.	F	6½	0	0		Control	47.0	13.5
			0	50 mg. i.v.		Control	70.5	9.0
			0	100 mg. i.m.		3 days	55.0	12.6
			16.6 mg. i.m.	0		1–12	24.5	3.0

* "Days of study" are numbered from the first day of cortisone or compound F therapy (except in Case 6). The period before therapy is called the control period. The values for estrogens and 17-KS are the average of all the determinations made during the periods indicated.

2. *Congenital adrenal hyperplasia*

In Tables 2 and 3 are recorded the findings in 13 cases of congenital adrenal hyperplasia. Additional data of these cases have been reported elsewhere (15). Seven of these were female pseudohermaphrodites between the ages of $6\frac{1}{2}$ to 49 years, 3 were males with macrogenitosomia precox between the ages of $3\frac{1}{2}$ and 9 years, and 3 were female pseudohermaphrodites studied during the first year of life. In addition, studies were made on

TABLE 3. EFFECT OF CORTISONE, ACTH AND COMPOUND B ON URINARY ESTROGENS IN CONGENITAL AND ACQUIRED ADRENAL HYPERPLASIA

Case	Sex	Age	Treatment			Days of study*	Urinary fluorogenic estrogens (γ/av. per 24 hrs. as α-estradiol)	Urinary 17-KS (mg./av. per 24 hrs.)
			Cortisone	ACTH	Other			
Female Pseudohermaphrodites under 1 year of age								
11/F.F.	F	4 mos.	0	0	Salt added	Control	15.0	4.2
			12.5 mg. (oral)	0	Salt added	70–115	6.7	1.1
12/K.S.	F	3 mos.	0	0	Salt added	Control	18.5	3.8
			8 mg. i.m.	0	Salt + DCA	70–85	5.6	0.2
13/L.U.	F	7 wks.	0	0	125 mEq. Na	Control	26.5	3.5
			25 mg. i.m.	0	125 mEq. Na	1–66	10.4	0.3
			25 mg. i.m.	0	0	67–113	6.3	0.4
			5 mg. i.m.	0	0	114–119	17.6	1.7
			5 mg. i.m.	0	100 mEq. Na	120–183	7.3	0.3
			5 mg. (oral)	0	100 mEq. Na	184–226	2.9	0.5
			0	0	100 mEq. Na	227–259	47.1	3.5
			0	0	100 mEq. Na Cpd. B, 12.5 mg. i.m.	300–371	11.8	1.2
Macrogenitosomia Precox								
14/D.B.	M	9 yrs.	0	0		Control	107.0	23.0
			0	50 mg. i.v.		Control	96.0	39.5
			50 mg. i.m.	0		7–9	32.0	5.0
15/A.B.	M	4 yrs.	0	0		Control	24.0	7.7
			0	50 mg. i.v.		Control	32.5	9.7
			50 mg. i.m.	0		3–6	16.0	1.7
16/W.D.	M	3½ yrs.	0	0		Control	62.6	17.8
			0	50 mg. i.v.		Control	56.5	45.7
			75 mg. (oral)	0		1–11	44.2	7.0
			50 mg. (oral)	0		12–21	19.0	4.2
			50 mg. (oral)	50 mg. i.v.		22	22.5	9.9
Acquired Adrenal Hyperplasia								
17/J.J.	F	22 yrs.	0	0		Control	116.0	32.5
			50 mg. i.m.	0		1–12	41.0	6.9
			100 mg. (oral)	0		13–18	56.0	4.7
			75 mg. (oral)	0		19–30	33.7	4.8

* "Days of study" are numbered from the first day of cortisone therapy. The period before therapy is called the control period. The values for estrogens and 17-KS are the average of all the determinations made during the periods indicated.

a female of 22 years in whom virilization developed during adolescence. In the 7 older female pseudohermaphrodites the output of fluorometrically determined estrogens varied from 47 to 212 micrograms per twenty-four hours—values which were as high or higher than those found in the patients with adrenal tumors. The 17-ketosteroids varied from 13.5 to 68

mg. per twenty-four hours. The males with macrogenitosomia precox excreted from 24 to 107 micrograms of fluorometrically measured estrogens and from 7.7 to 23 mg. of 17-ketosteroids per twenty-four hours. The infant female psuedohermaphrodites excreted from 15 to 26.5 micrograms of fluorometrically measured estrogens and from 3.5 to 4.2 mg. of 17-ketosteroids per twenty-four hours. The patient with the non-congeni-

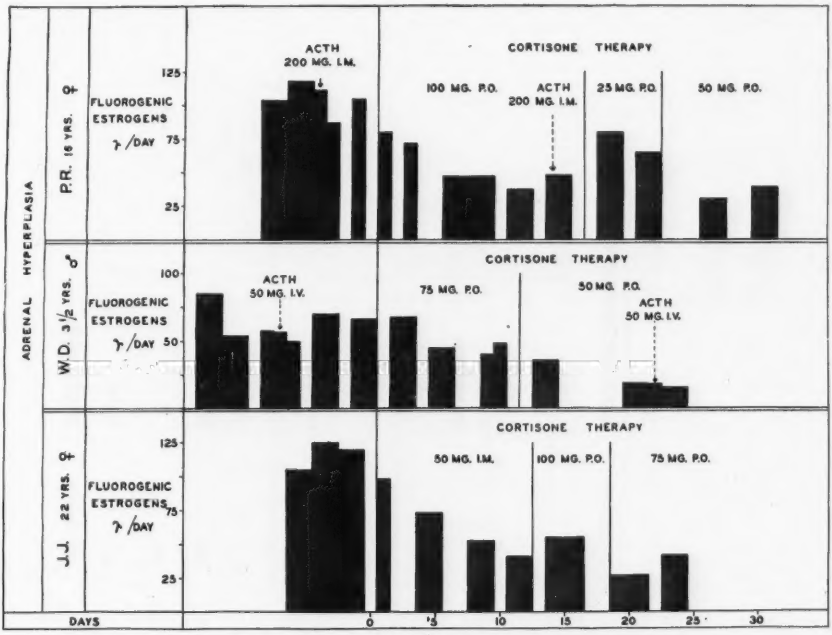

FIG. 4. Urinary excretion of fluorometrically measured estrogens in 2 cases of congenital adrenal hyperplasia (P. R., Case 7; and W. D., Case 16) and in 1 case of acquired adrenal hyperplasia (J. J., Case 17). Adequate cortisone treatment brought down to a normal level the increased urinary fluorogenic estrogens.

tal type of adrenal hyperplasia (J.J., Case 17) had an average daily output of 116 micrograms of fluorometrically measured estrogens (Table 3) and 32.5 mg. of 17-ketosteroids. Thus high excretions of fluorometrically measured estrogens as well as 17-ketosteroids were found in all cases, but there was no consistent ratio between the amounts of these two groups of steroids.

The effects of ACTH were studied in 8 cases before cortisone therapy (Cases 6, 7, 8, 9, 10, 14, 15 and 16). In 2 instances (Cases 9 and 10) there was an increase of the fluorometrically measured estrogens but in the other patients no change. The urinary excretion of 17-ketosteroids increased in

3 patients (Cases 9, 14, 16). During cortisone therapy, the administration of ACTH increased the output of estrogens in Cases 7 and 8 and that of 17-ketosteroids in Cases 8 and 16. The differences in results are difficult to interpret.

Under cortisone therapy the daily 17-ketosteroid excretion was reduced to levels of 4 to 6 mg. in all of the patients over 3 years, and in the young infants to 0.3 to 0.8 mg. Studies of urinary excretion of fluorometrically

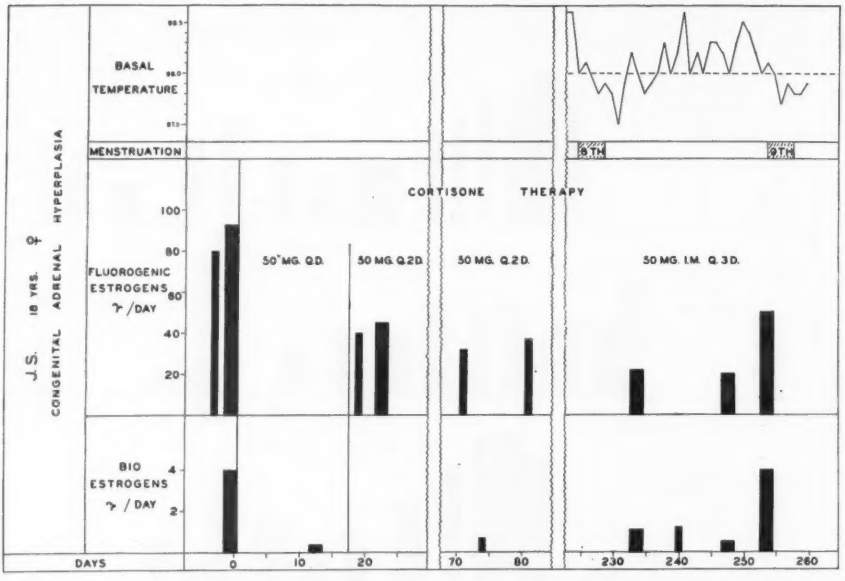

FIG. 5. Study of fluorogenic and bio-estrogens in a female pseudohermaphrodite (Case 5) before, and at different stages of cortisone therapy.

measured estrogens made at various stages of cortisone therapy showed that these steroids were reduced along with the 17-ketosteroids as indicated in Tables 2 and 3. However, there was no constant ratio between these two groups of steroids. In the older females the output of fluorometrically measured estrogens did not fall below levels of 28 to 39 micrograms per twenty-four hours (Fig. 4). In the males the values of 16, 19, and 32 micrograms per twenty-four hours were observed. In the infant pseudohermaphrodites the output varied from 2.9 to 7.3 micrograms per twenty-four hours.

Treatment with compound F in Patient M. N. (Case 8) and compound B in Patient L. U. (Case 13) caused a decrease of fluorometrically measured estrogens and 17-ketosteroids similar to that brought about by cortisone.

In Patient J. S. (Case 5) bioassays for estrogens were made in addition

to the fluorometric determinations. Before treatment the patient excreted 53 mg. of 17-ketosteroids and 93 micrograms of estrogens determined fluorometrically, whereas the biologic assay showed an estrogenic activity equivalent to 4 micrograms of α-estradiol per twenty-four hours. About twenty days after starting cortisone therapy the urinary 17-ketosteroids

TABLE 4. EFFECT OF CORTISONE ON URINARY ESTROGENS IN CUSHING'S SYNDROME AND IN A NORMAL MALE ADULT

Case	Sex	Age (yrs.)	Clinical type	Treatment	Days of study*	Urinary fluorogenic estrogens (γ/av. per 24 hrs. as α-estradiol)	17-KS (mg./av. per 24 hrs.)
				Cushing's Syndrome			
18/H.G.	F	42	Malignant adrenal tumor with metastases	None	1–8	87.7	35.0
				Cortisone, 50 mg. i.m.	9–21	142.5	35.5
				Cortisone, 100 mg. i.m.	22–26	124.0	43.1
				None	27–42	73.5	38.0
19/P.S.	F	10	Idiopathic	None	1–13	29.7	11.4
				Cortisone, 50 mg. i.m.	14–31	28.3	11.2
				None	32–41	21.3	9.6
20/J.T.	M	41	Idiopathic	None	1–8	44.2	14.4
				Cortisone, 100 mg. i.m.	9–20	53.0	19.0
21/K.H.	M	35	Idiopathic	None	1–5	32.0	18.7
				Cortisone, 100 mg. i.m.	6–15	38.5	13.7
				Normal Male Adult			
C.M.	M	27		None	1–8	29.5	10.7
				Cortisone, 75 mg. (oral)	9–23	26.5	10.1
				None	24–29	32.5	10.2

* "Days of study" are numbered from the day when the investigations were begun. The values for estrogens and 17-KS are the average of all the determinations made during the periods indicated.

had fallen to a level of 4.1 mg. per twenty-four hours. At this time, the fluorometrically measured estrogens were 40 micrograms per twenty-four hours, whereas the bioassay showed an estrogenic activity equivalent to 0.4 microgram of α-estradiol. This patient's breasts developed and the vaginal smear showed estrinization. She menstruated for the first time thirty-two days after starting cortisone therapy. Estrogen excretion was studied during the period between the eighth and ninth menstrual periods (225 to 254 days after beginning cortisone treatment), as shown in Figure 5.

3. *Cushing's syndrome*

The study on 4 patients with Cushing's syndrome is shown in Table 4. One of these patients (Case 18) had a malignant adrenal tumor with

metastases. J. T. and K. H. (Cases 20 and 21)[2] had characteristic obesity, hirsutism, hypertension and generalized osteoporosis but a normal glucose tolerance curve. P. S. (Case 19) was a 10-year-old female with obesity, hirsutism and acne, whose 17-ketosteroid excretion ranged from 6 to 16 mg. per twenty-four hours, with an average of 11 mg. She had a normal

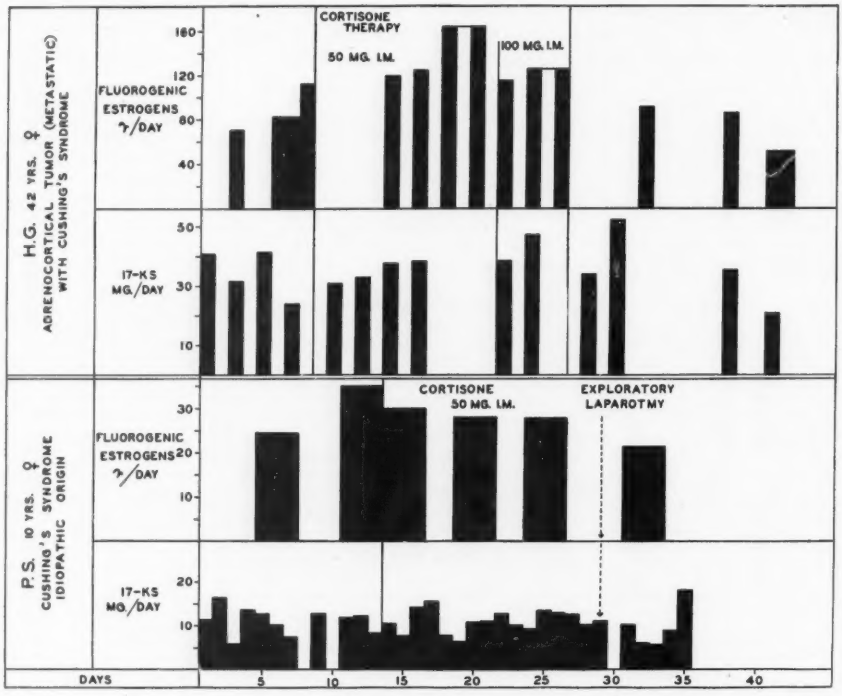

FIG. 6. Urinary steroids in Cushing's syndrome due to adrenocortical tumor (Case 18) or of idiopathic origin (Case 19). Cortisone administration had no significant effect on steroid excretion.

glucose tolerance curve and no hypertension. Exploration of the abdomen revealed no adrenal tumor.

The patient with the malignant adrenal tumor excreted 88 micrograms of fluorometrically measured estrogens and 35 mg. of 17-ketosteroids per twenty-four hours (Fig. 6). The administration of large doses of cortisone had no effect on the 17-ketosteroids, but there was some increase of the fluorometrically measured estrogens. The urinary 17-ketosteroids were not significantly increased in the 2 males with Cushing's syndrome, being

[2] These patients were studied by the authors through the courtesy of Dr. John Eager Howard.

14.4 and 18.7 mg. per twenty-four hours. The urinary excretion of fluorometrically measured estrogens was 44 and 32 micrograms per twenty-four hours. Cortisone had no effect on either 17-ketosteroids or fluorometrically measured estrogens. The output of 17-ketosteroids of the 10-year-old girl was higher than normal for her age. The fluorometrically measured estrogens were 29.7 micrograms per twenty-four hours. Cortisone administration did not have any effect on either the estrogens or the 17-ketosteroids.

4. *Adult male control*

A normal male, aged 27 years, received oral cortisone, 50 mg. for one day and 75 mg. per day for thirteen days. There was no definite change either in the urinary excretion of fluorometrically measured estrogens or of 17-ketosteroids. The urinary reducing corticoids showed a rise during cortisone administration but returned to a normal level after its cessation.

DISCUSSION

The amounts of urinary estrogens reported by various workers in cases of virilizing adrenocortical tumors cannot be compared because of differences in the methods employed. The very high values reported by Franck and others (16–20), considered at one time to be diagnostic of malignant adrenal carcinoma, may have been due to the fact that these workers assayed unextracted urine by its effect on the vaginal smear of castrated rats. Some workers (21–24) making bioassays on the phenolic fraction of urinary extracts in cases of adrenal tumor found relatively normal amounts of estrogens, whereas others (25, 26) reported an increased amount. Using a chemical fractionation, Burrows and colleagues (27) found in a case of malignant tumor of the adrenal cortex 3,000 I.U. of estrogenic substances measured biologically in the "more soluble semicarbazones from the ketonic phenolic fraction." Estrone was not identified, but if it was present it should have appeared in this fraction. Mason and Kepler (28) isolated 62 mg. of estrone from twenty-six days' pooled urines of a case of adrenocortical tumor. The amount of estrone accounted for only 35 per cent of the total estrogenic activity determined by bioassay. Estradiol and estriol were not found. The tumor itself contained a total estrogenic activity equivalent to 268 micrograms of estrone as determined by bioassay (communicated data).

The fluorometric method of Jailer is an attempt to measure the total amount of phenolic steroids excreted in the urine.[3] Its accuracy depends

[3] Jailer's method was modified by using 1 N NaOH for extracting benzene, since the partition ratio of estrone is more favorable to the benzene phase when 2 N NaOH is used (29). A modification was made also in the technique for the production of fluorescence, as advised by Bates and Cohen (30–31).

upon: a) the completeness of extraction of the steroids after hydrolysis of their conjugates, and b) separation of the steroids from all other substances which might give rise to fluorescence. In the human subject the principal phenolic steroids excreted are estradiol, estrone and estriol. These differ in their solubility in benzene, and it is probable that estriol is not completley extracted by the method employed. Although many other steroids and pigments may give rise to fluorescence, it is improbable that they would be found in more than traces in the phenolic fraction. An inherent difficulty in the method, however, lies in the fact that the fluorogenic potencies of estradiol and estrone differ considerably from that of estriol (Table 5). Also the biologic activity of the three compounds varies and is unrelated to their fluorogenic potency. Accordingly, if one assays two mixtures containing the same total amount of phenolic steroids but varying in the proportions of estradiol, estrone and estriol, one may

TABLE 5. RELATIVE POTENCY OF THE DIFFERENT ESTROGENS DETERMINED BY FLUOROMETRIC AND BIOLOGIC METHODS, EXPRESSED IN PERCENTAGE OF ESTRONE ACTIVITY

Estrogenic substances	Fluorometric method	Biologic method	
		(9)*	(32)*
Estrone	100	100	100
α-Estradiol	63	300	545
Estriol	72	40	5

* From the data of Evans *et al.* (9) and of Rubin *et al.* (32).

find marked differences in both their fluorometric values and their biologic activities. These may be quite unrelated to each other. A fuller knowledge of estrogen secretion in adrenal disorders must await the application of more precise methods for the quantitative separation of the estrogenic steroids.

Our laboratory agrees with the reports of Jailer that normal, adult females excrete 25–50 micrograms of fluorometrically determined estrogens per twenty-four hours, adult males 20–45 micrograms, and children 5–15 micrograms. In the 3 cases of adrenal virilizing tumor, all without metastasis, the fluorometric estrogens were moderately increased. The adult female excreted 84.5 micrograms per twenty-four hours and the children 79.6 and 45.8 micrograms. The patients with congenital or acquired adrenal hyperplasia excreted equally large or even greater amounts; the patients $3\frac{1}{2}$ to $18\frac{1}{2}$ years old put out 62.6 to 212 micrograms per twenty-four hours, and an infant of a few months 26.5 micrograms. It is apparent, therefore, that the amount of fluorometrically determined estrogen excreted in the

untreated patient does not help to differentiate virilizing adrenal tumor from adrenal hyperplasia. In a case of Cushing's syndrome due to a malignant adrenal tumor with metastases, the estrogens were moderately elevated, whereas in 3 cases of Cushing's syndrome not due to adrenal tumor, they were within normal range.

In our experience, the administration of cortisone to patients with adrenal hyperplasia decreased markedly the output of fluorometrically measured estrogens, whereas in patients with adrenal tumors causing either hirsutism, virilization or Cushing's syndrome, the output was unaffected. Likewise, the excretion of estrogens was not affected in cases of Cushing's syndrome without tumors. When the adrenal tumors were removed, the estrogens fell to 31–46 per cent of their previous values, and the 17-ketosteriods to 1–10 per cent. In the cases of congenital adrenal hyperplasia, cortisone therapy reduced the estrogens to 13–42 per cent (with an average of 38 per cent of the pretreatment levels), whereas the 17-ketosteroids fell to 9–24 per cent with an average of 14 per cent. In general, the estrogens increased and decreased concomitantly with the 17-ketosteroids. However, there was no constant ratio between the two groups of steroids. These findings suggest that, in the cases studied, the fluorometrically measured estrogens were derived from the adrenals rather than from the ovaries.

The experiments did not provide any direct evidence that the chemically determined estrogens were influenced by ACTH. In only 1 case, Patient H. B. who had an adrenal tumor, was there a slight increase of estrogen, as well as of 17-ketosteroids, when ACTH was given intravenously.

The studies yield relatively little information on the nature of the estrogens measured fluorometrically. In 2 cases of adrenal tumor and in 1 of congenital hyperplasia, bioassays for estrogen were made simultaneously with the chemical determinations. The values found in the cases of tumor, 14 and 16 micrograms per twenty-four hours, were high for normal adults (equivalent to 140 and 160 I.U.). The value of 4 micrograms (or 40 I.U.) found in the case of congenital adrenal hyperplasia was within the normal adult range. It is evident that when both the fluorometric value and the biologic activity are referred to the equivalent of α-estradiol, the amount of biologic activity is far less than would be expected from the fluorometric potency, if this were due entirely to α-estradiol. It would seem, therefore, that a large fraction of the material measured fluorometrically must be estrogens of considerably lower biologic activity than α-estradiol, or else non-estrogenic substances causing fluorescence. In Patient E. H. removal of the tumor caused the fluorometrically determined estrogens to fall to 41 per cent and the biologically measured estrogens to 8 per cent of the previous values. In Patient H. B. (a boy of $4\frac{3}{4}$ years) the fluorogenic estro-

gens fell to 12 per cent and the biologic estrogens to 2 per cent. In J. S., who had congenital adrenal hyperplasia, treatment with cortisone caused a decrease in the fluorogenic estrogens to 43 per cent and in the biologic estrogens to 10 per cent of the pretreatment levels. These findings suggest that the types of steroids being measured in the extracts studied, were altered by removal of the tumor or suppression of the adrenal by cortisone. It would appear that the steroids which were more active biologically were decreased to a greater extent than were those which were relatively inert.

The effects of cortisone treatment upon the estrogen excretion of J. S., a female pseudohermaphrodite who became feminized and established regular menstrual cycles, is of particular interest. After she had been treated with cortisone for 225 days and had had 8 menstrual periods, a number of determinations of estrogens were made during the ensuing cycle. On the pooled urines of the day before and the first day of the next period, the daily urinary excretion of estrogens was 40 micrograms (fluorometrically measured) and 4 micrograms as α-estradiol (biologically measured). In the early part of this cycle the daily fluorometrically measured estrogens were 20.5 to 22.5 micrograms, the corresponding values for the daily biologically measured estrogens being the equivalent of 0.55 to 1.17 micrograms of α-estradiol. This increase of the biologically measured estrogens, after their reduction to 0.4 microgram on the nineteenth day of treatment, is probably due to the cyclic secretion of estrogens by the ovaries.

In the 3 cases of Cushing's syndrome without adrenal tumor, the fluorometrically measured estrogens of the urine were not increased nor were they influenced by the administration of cortisone. Dorfman (39) did not find an increase in urinary estrogens measured by bioassay in 3 cases of Cushing's syndrome.

In the patient with a malignant adrenal tumor, there was a moderately increased excretion of both fluorometrically measured estrogens and 17-ketosteroids.

SUMMARY

1. In 3 cases of adrenocortical tumor of virilizing or hirsutizing type, the urinary excretion of fluorometrically determined estrogens was increased. Administration of cortisone did not decrease the excretion. The effect of ACTH was variable.

2. In 14 cases of adrenal hyperplasia (10 female pseudohermaphrodites, 3 macrogenitosomia precox, 1 acquired adrenal hyperplasia), the urinary excretion of fluorometrically measured estrogens was also increased. Cortisone therapy caused a prompt decrease of the excretion. Compound B and compound F had the same effect in less degree. The effect of ACTH was variable.

3. In 1 case of Cushing's syndrome due to a malignant adrenocortical tumor with metastasis, the urinary excretion of fluorometrically measured estrogens was increased. In 3 other cases of Cushing's syndrome without adrenal tumor, it was within normal limits. Cortisone administration did not cause any change in the values of urinary estrogens of the 4 cases.

4. Cortisone administration did not change the excretion of fluorometrically measured estrogens of a control adult male.

5. The sharp drop of urinary estrogens under cortisone therapy, like the drop of urinary 17-ketosteroids, seems to be characteristic of congenital or acquired adrenal hyperplasia. This fact is of interest in the differentiation of adrenal hyperplasia and adrenocortical tumor.

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EFFECTS OF CHORIONIC GONADOTROPIN (APL) IN MALE "EUNUCHOIDISM WITH LOW FOLLICLE-STIMULATING HORMONE": AQUEOUS SOLUTION VERSUS OIL AND BEESWAX SUSPENSION*†

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MALE eunuchoidism with low follicle-stimulating hormone (FSH) (1, 2, 3) is characterized by hypogonadism with virtual absence of secondary sex characteristics, normal somatic growth except for the changes attributable to delayed epiphyseal closure, testicular tissue either characteristic of the normal prepubertal state or differing therefrom by thickening of the tunica propria and, of course, low[1] or absent urinary FSH titers. Urinary 17-ketosteroids are present in subnormal amounts.

It has been established that therapy with chorionic gonadotropin in this syndrome will produce secondary sex characteristics (3), raise the 17-ketosteroid excretion (5), and produce partial maturation of the Leydig cells and tubules (3). It has been denied (3, 6), however, that chorionic gonadotropin has a direct influence on spermatogenesis.

In the present study, a comparison is made between the effects of an aqueous solution of APL[2] and those of the same material suspended in a base of peanut oil and beeswax. In addition, the effects of protracted therapy in 3 patients are reported. The indices chosen for measuring results were the urinary 17-ketosteroids and the histologic appearance of the testis as judged from serial biopsies. In addition, repeated counts of spermatozoa in seminal fluid were made in the long-term studies.

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[1] In this clinic, normal males have been found to excrete 13 or more mouse units per twenty-four hours. A single exception excreted over 6.6 but less than 13 mouse units per twenty-four hours (4).

[2] "APL" is the trade name for chorionic gonadotropin produced by Ayerst, McKenna and Harrison, Ltd., who supplied all the material used in this study through the courtesy of Dr. Edward C. Reifenstein, Jr. and Dr. Stanislas Jaros. The aqueous preparation was Product No. 999 of Ayerst, McKenna and Harrison, Ltd.

METHODS

17-Ketosteroids were measured by a modification (5) of the method of Callow, Callow and Emmens (7). Eight-hour urine specimens collected on two consecutive nights were pooled for a single determination.

Testicular biopsies and spermatozoa counts were performed as previously described (2).

All injections were given intramuscularly. Table 1 shows the design of each of the short-term experiments, wherein comparisons of the two preparations were made. In Cases 1 through 7 a course of aqueous APL, given once or twice a day, was compared with a course of APL in oil and beeswax given once every two to five days. In Case 9 a course of aqueous APL, given once or twice a week, was compared with a course of APL in oil and beeswax similarly administered; in Case 8 two courses of APL in oil and beeswax were compared with two courses of aqueous APL, one given five times a week, the other once a week.

TABLE 1. SYNOPSIS OF TREATMENT—SHORT-TERM EXPERIMENTS

Case No.	Initials	M.G.H. unit No.	Therapy
1	N.F.	156629	Water 1,250 b.i.d., then oil 5,000 q.2 d.
2	S.C.	576949	Water 2,500 q.d., then oil 5,000 q.2 d.
3	C.A.	407367	Water 1,250 b.i.d., then oil 5,000 q.2 d.*
4	F.O.	61709	Water 1,000 q.d., then oil 5,000 q.5 d.*
5	N.C.	190543	Water 1,000 q.d., then oil 5,000 q.5 d.
6	E.F.	223607	Oil 5,000 b.i.wk., then water 2,000 q.d. (6d/wk.)
7	A.L.	617234	Oil 5,000 q. 3 d., then water 1,550 q.d.*
8	J.C.	682536	Water 5,000 q.wk., then oil 5,000 q.wk., then water 1,000 5 q.wk., then oil 5,000 q.wk.
9	E.C.	687550	Water 5,000 q.wk., then oil 5,000 q.wk., then water 5,000 b.i.wk., then oil 5,000 b.i.wk.

* *See* text for protracted studies on these patients.

SUBJECTS

Table 2 gives some of the salient clinical findings in each patient studied. All patients when first seen showed small testes, a very small prostate, underdevelopment of phallus and scrotum, absence of beard, diminished or absent axillary and pubic hair, high pitched voice with small thyroid cartilage, and failure of temporal recession of the hairline.

RESULTS

Results are shown graphically in Figures 2–10. Figure 1 indicates the method employed for recording the appearance of the testicular biopsy

specimens, diagram 1 representing a typical[3] specimen before therapy, diagram 3 a fully matured adult testis, and diagram 2 a stage intermediate between 1 and 3. The method of grading biopsies is indicated in the legend to Figure 1.

I. Short-term studies

1. N. F. (Fig. 2). The second course (oil)[4] produced a slight and unconvincing rise in 17-ketosteroid excretion; the first (water) produced no rise. The testicular biopsy showed only slight maturation during the first course, but definite maturation during the second.

TABLE 2. CLINICAL DATA PERTINENT TO THE CASES REPORTED

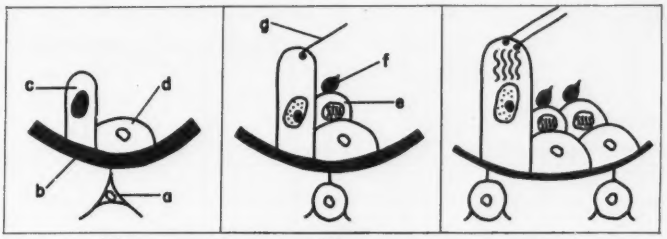
Case No.	Age (yrs.)	Height (in.)	Span (in.)	FSH, m. u. 24 hrs.	17-KS before treatment, mg./24 hrs.	Sella turcica (x-ray exam.)	Bone age (yrs.)	Remarks
1	22	66¼	69	neg. 6.5	0.9	small	17	Testosterone and APL 3 yrs. before study. ITT* normal.
2	18½	60¾	63½	neg. 6.5	3.1	normal	12	
3	17½	69½	74½	neg. 6.5	1.7, 2.8	normal	13	ITT normal.
4	28	70¾	74¾	neg. 6.5 pos. 3	6.8, 4.4	normal	21	
5	23	67½	72	pos. 6.5 neg. 13	6.2, 3.9	normal	14½	Testosterone 4 yrs. before study.
6	21	67½	69½	neg. 6.5 pos. 3	3.7	normal	15½	
7	31	72½	73	neg. 6.5	9.1, 8.4	small	17†	Testosterone 10 yrs. before study
8	23	66	68	pos. 6.5 neg. 13	2.6, 2.5	small	15½	
9	18	87½	70	neg. 6.5	2.7, 3.2	normal	14½	

* Insulin tolerance test.
† At age 21. Epiphyses fused during testosterone therapy before present study.

APL in oil, in a dosage of 5,000 units a week, produced a definite rise in the average 17-ketosteroid excretion; its discontinuance was followed by a fall.

2. S. C. (Fig. 3). Both the first course (water) and the second (oil) produced clear rises in 17-ketosteroid excretion. The testicular biopsy (Fig. 11) showed no maturation during the first course, and definite maturation during the second, but the total dosage was greater in the second. APL in oil, in a dosage of 5,000 units a week, did not produce an unequivocal rise in 17-ketosteroids. When therapy was discontinued, the testicular biopsy showed reversion to the immature state (Fig. 11).

[3] But see subsequent discussion of thickening of tunica propria.
[4] Suspension in oil and beeswax is hereafter designated "oil."



	1	2	3
LEYDIG CELLS	0	+	+ +
TUNICA PROPRIA	+ +	+	N
SERTOLI CELLS	0	+	+ +
SPERMATOGONIA	+	+	+ +
SPERMATOCYTES	0	+	+ +
SPERMATIDS	0	+	+ +
SPERMATOZOA	0	+	+ +

FIG. 1. Schematic diagram to illustrate method used in Figures 2–10 for grading testicular biopsies. Three grades of maturity (1, 2, 3) have been chosen for each element (except spermatogonia). 1. Completely immature testis of eunuchoidism-with-low-FSH. 2. Stage of maturation intermediate between grades 1 and 3. 3. Mature testis. a) Leydig cell. Note that maturation is shown as increase in size and in numbers. b) Tunica propria. In the diagram, it is shown abnormally thick in eunuchoidism-with-low-FSH. In some cases it is normal. For thinning with maturation, *see* text. c) Sertoli cell. Maturation is shown as increase in cytoplasm, with appearance of "fibrils," vesiculation of nucleus, and emergence of nucleolus. d) Spermatogonia. e) Spermatocytes. Primary and secondary spermatocytes are included. f) Spermatids. g) Spermatozoa.

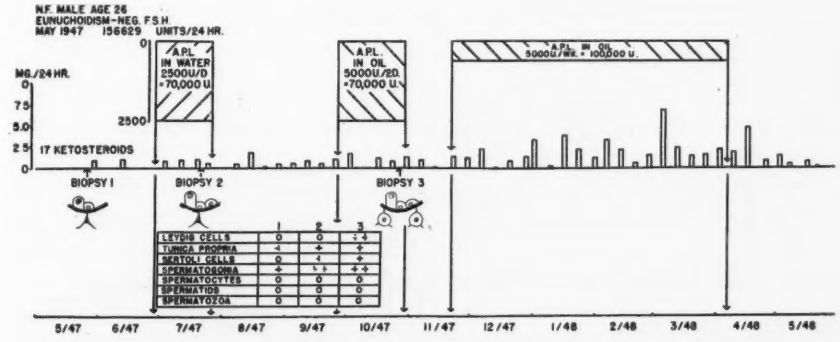


FIG. 2. Treatment, 17-ketosteroid excretion, and testicular histologic pattern in Case 1. Time is plotted as the abscissa. Height of treatment columns is proportional to daily dosage, and thus area represents total dosage. For description of testicular structure, *see* legend to Figure 1.

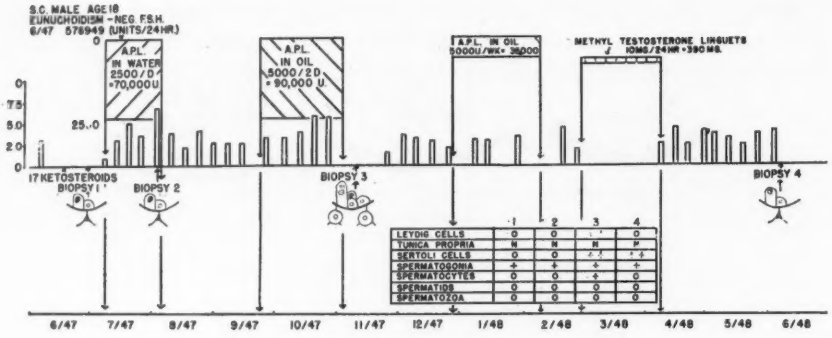


FIG. 3. Data on Case 2. (*See* also Fig. 11, and legends to Figs. 1 and 2.)

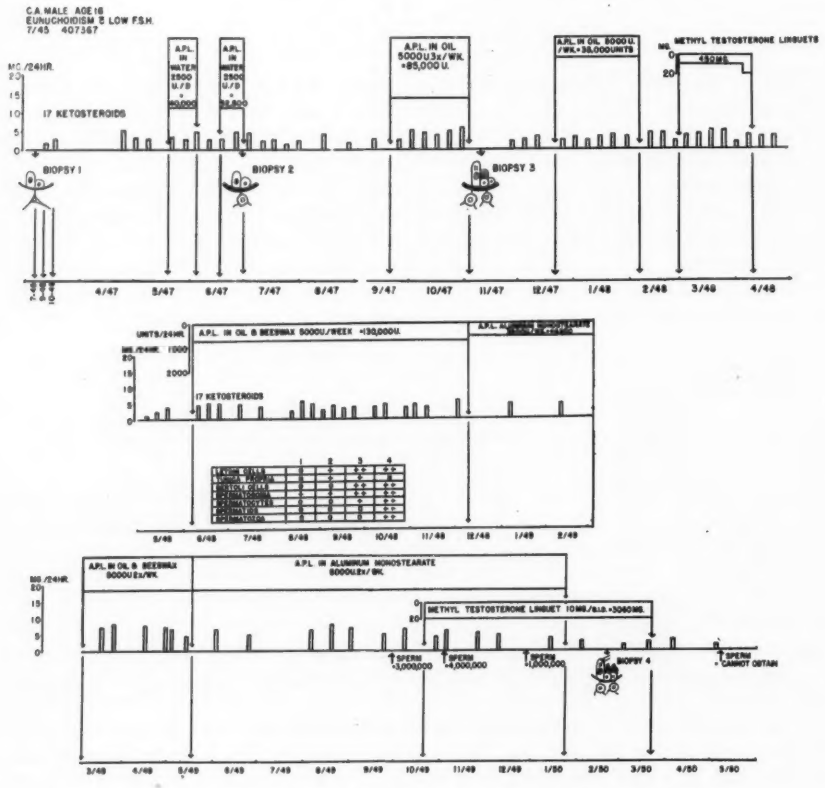

C.A. MALE AGE 18
EUNUCHOIDISM & LOW F.S.H.
7/45 407367
A.P.L. IN WATER 2500 U/D
A.P.L. IN OIL 5000U 3x/WK. =85,000 U.
A.P.L. IN OIL 5000 U./WK.=35,000UNITS
METHYL TESTOSTERONE LINGUETS
17 KETOSTEROIDS
BIOPSY 1
BIOPSY 2
BIOPSY 3
4/47 5/47 6/47 7/47 8/47 9/47 10/47 11/47 12/47 1/48 2/48 3/48 4/48
A.P.L. IN OIL & BEESWAX 5000U/WEEK =130,000U.
17 KETOSTEROIDS
A.P.L. IN OIL & BEESWAX 5000U Ex/WK.
A.P.L. IN ALUMINUM MONOSTEARATE 5000U Ex/WK.
METHYL TESTOSTERONE LINGUET 10MG/D.U.D. =350MG.
SPERM =3,000,000
SPERM =4,000,000
SPERM =1,000,000
BIOPSY 4
SPERM = CANNOT OBTAIN

FIG. 4. Data on Case 3. (*See* also Fig. 14, and legends to Figs. 1 and 2.)

3. C. A. (Fig. 4). Both the first course (water) and the second (oil) produced slight rises in 17-ketosteroid excretion. The testicular biopsy (Fig. 14) showed slight maturation during the first course, and considerable maturation during the second. (For the remainder of study in this patient, *see* section II, Case 1.)

4. F. O. (Fig. 5). Both the first course (water) and the second (oil) produced rises in 17-ketosteroid excretion. The testicular biopsy (Fig. 16) showed *slight maturation before therapy*, no increase during the first course, and a slight increase during the second. (For the remainder of study in this patient, *see* section II, Case 3.)

In these 4 cases, APL in oil appeared to have *at least* as great an effect on 17-ketosteroid excretion as equivalent doses of APL in water given at

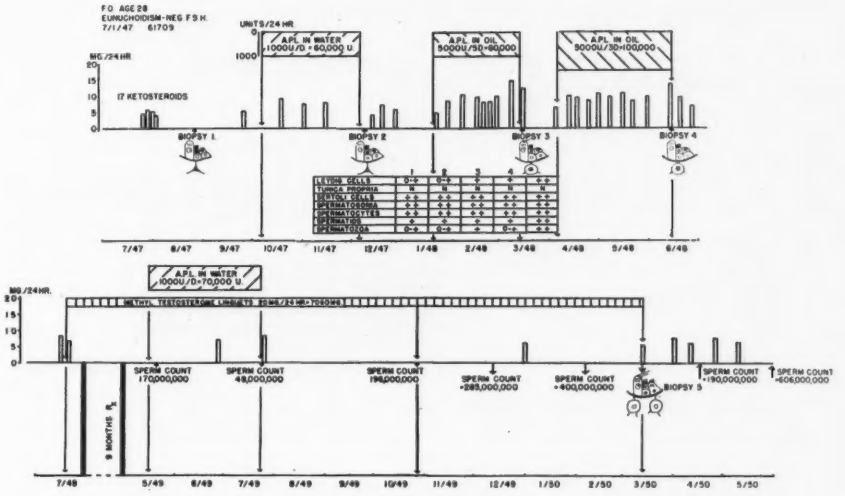


FIG. 5. Data on Case 4. (*See* also Fig. 16, and legends to Figs. 1 and 2.)

more frequent intervals. The testes showed greater maturation after the APL in oil. However, the data do not exclude the possibility that the apparent advantage of the oily preparation may result from the initial stimulus supplied by the preceding course of aqueous APL. Therapy in Case 5 was designed so as to obviate this objection. In Cases 6 and 7 the order of administration was reversed.

5. N. C. (Fig. 6). Neither the first course (water) nor the second (oil) produced an unequivocal rise in 17-ketosteroid excretion. The testicular biospy (Fig. 12), which had showed some maturation during the first course, *showed reversion to the initial state* four months later; the maturation was somewhat greater during the second (oil) course. The tunica propria was thickened initially, and became normally thin during treatment (Fig. 12). APL in water, in a dosage of 500 units a day, did not produce an unequivocal rise in 17-ketosteroid excretion.

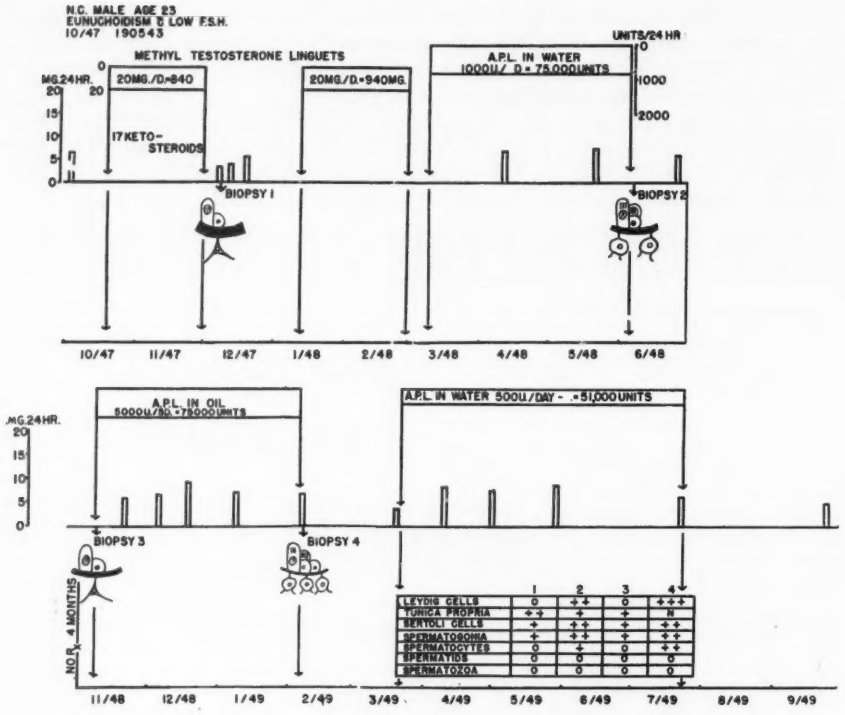


FIG. 6. Data on Case 5. (*See* also Fig. 12, and legends to Figs. 1 and 2.)

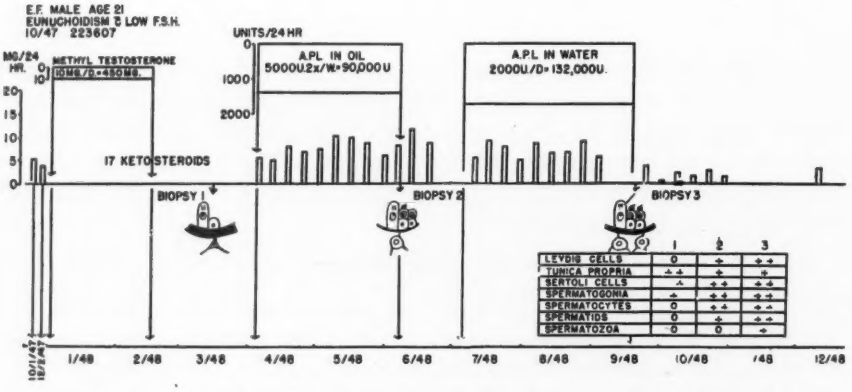


FIG. 7. Data on Case 6. (*See* also Fig. 13, and legends to Figs. 1 and 2.)

In this case, in which a four-month interval was allowed between courses, and a new "control" biopsy was performed, the effects of the oily preparation may be judged independently of those of the preceding aqueous APL. The oily preparation given at five-day intervals appeared to be as effective as the aqueous preparation given daily.

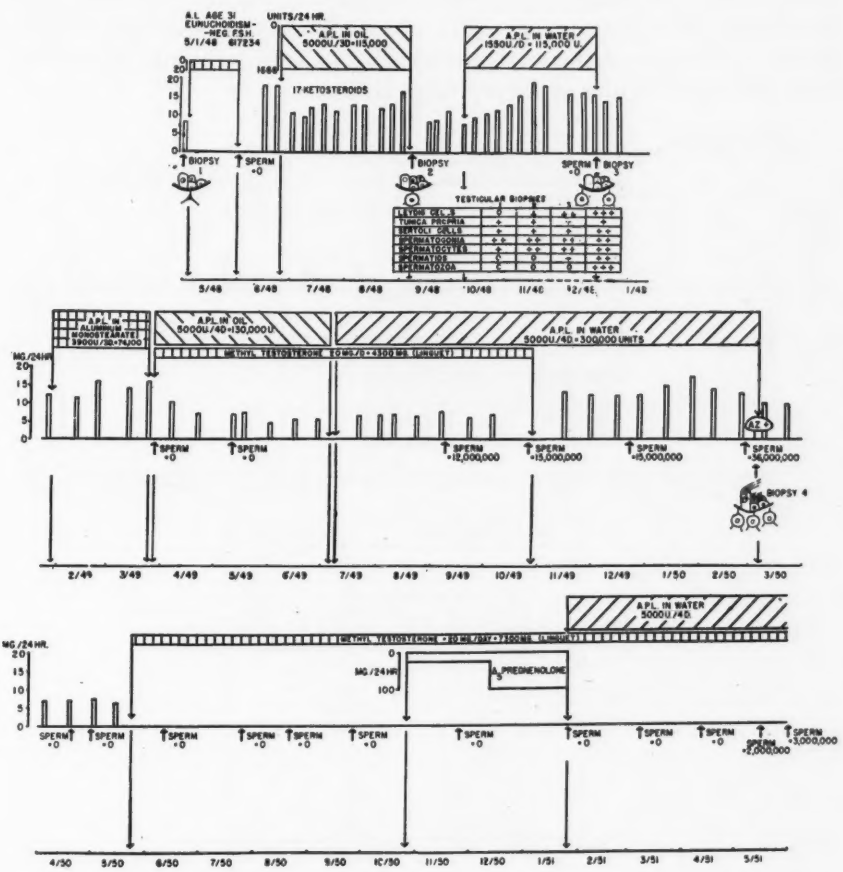


FIG. 8. Data on Case 7. (*See* also Fig. 15, and legends to Figs. 1 and 2.)

6. E. F. (Fig. 7). Both the first course (oil) and the second (water) produced rises in 17-ketosteroid excretion. The testicular biopsy (Fig. 13) showed some maturation during the first course, and increased maturation during the second; the duration and total dosage of therapy were greater in the second course. The tunica propria was thickened initially, and became thin on treatment (Fig. 13).

7. A. L. (Fig. 8). Both the first course (oil) and the second (water) produced rises[5] in 17-ketosteroid excretion. The testicular biopsy (Fig. 15) showed slight maturation during the first course and considerable maturation during the second. (For the remainder of study in this patient, *see* section II, Case 2.)

In these 2 cases, as in the preceding ones, APL in oil appeared to have as great an effect on 17-ketosteroid excretion as equivalent doses of aqueous APL given at more frequent intervals. The testis, however, showed greater maturation after the aqueous APL. This supports the belief that the apparent advantage of the oily preparation in Cases 1 through 4 resulted from the prior stimulus of the preceding course.

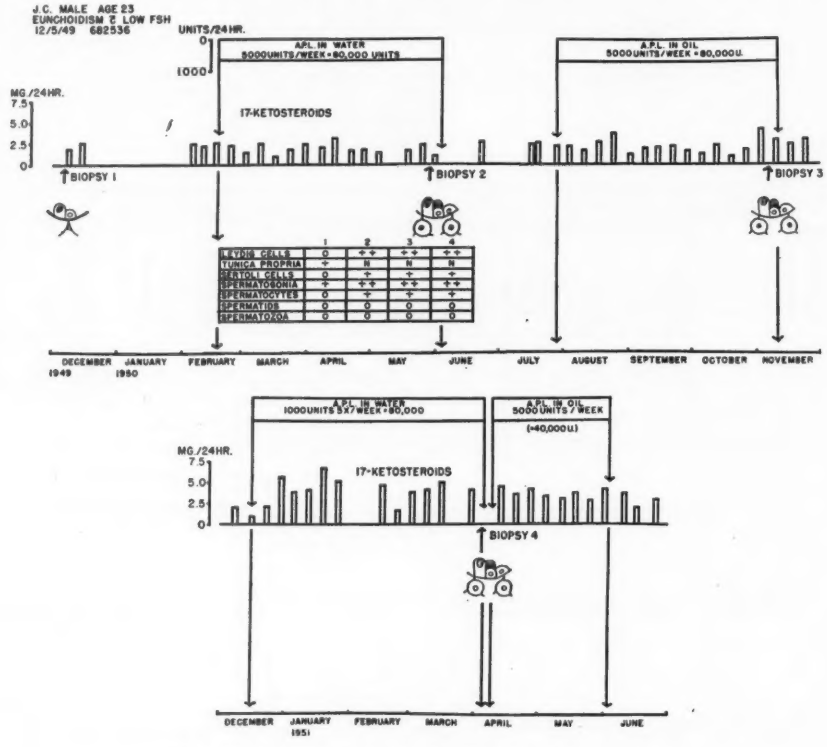


FIG. 9. Data on Case 8. (*See* legends to Figs. 1 and 2.)

[5] The two values for urinary 17-ketosteroids of 18 mg. per twenty-four hours, which were found just before the first course of therapy, are unexplained; no similar values have been found in this patient off therapy over a number of years. As they were assayed at the same time, they may represent a laboratory error; or they may represent a "rebound" of adrenal cortical 17-ketosteroid production following cessation of methyltestosterone therapy.

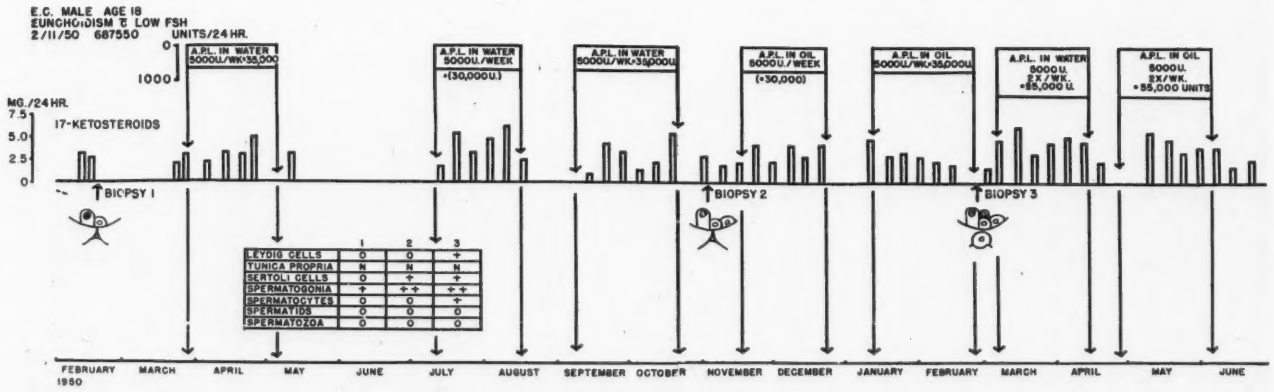


FIG. 10. Data on Case 3. (*See* legends to Figs. 1 and 2.)

From these studies it is apparent that the observed effects of aqueous APL given daily may be reproduced by the use of APL in oil given every second to fifth day. The question arises whether the aqueous preparation may not retain its effect when given at the wider intervals employed with the oily preparation. The results of long-term therapy in Case 7 (section II, Case 2) strongly suggested that such might be the case. Therapy in Cases 8 and 9 was designed to test this possibility.

8. J. C. (Fig. 9). The third course (water, five times weekly) produced a definite rise in 17-ketosteroid excretion; the first course (water, weekly) and the second (oil, weekly) did not.

The testicular biopsy showed definite maturation during the first course, but no further maturation during the second or third. When a fourth course (oil, weekly) was instituted in place of the third (water, five times weekly) the 17-ketosteroid excretion fell slightly. When all medication was stopped, it fell towards the initial control levels.

9. E. C. (Fig. 10). Neither the first[6] course (water, weekly) nor the second (oil, weekly) produced a sustained rise in 17-ketosteroid excretion. The testicular biopsy showed very slight maturation during the first course, and moderate maturation during the second. The third course (water, twice weekly) produced a definite rise in the average 17-ketosteroid excretion; when a fourth course (oil, twice weekly) was instituted in place of the third, the 17-ketosteroid excretion remained approximately unchanged. When all therapy was stopped, it fell to the initial control level.

In these 2 cases the initial dosage of APL was not high enough to produce marked changes in 17-ketosteroid excretion.[7] From the histologic evidence it is quite clear that even at weekly intervals aqueous APL exerts an effect on testis maturation. This was also evident clinically by enlargement of the testes and increased libido.

From the above observations it may be concluded that in the syndrome of eunuchoidism-with-low-FSH, APL in oil and beeswax given at two- to seven-day intervals is as effective as aqueous APL in equivalent total dosage, given daily. It has not been shown, however, that the oily preparation is *more* effective than the aqueous when both are given at four- to seven-day intervals.

II. *Long-term studies*

These were carried out in Patients 3, 4, and 7, following the short-term studies; the results are shown in Figures 4, 5, and 8.

1. C. A. (Fig. 4) (starting August 1948). APL in oil produced a slight rise in 17-ketosteroid excretion in a dosage of 5,000 units a week, and a moderate rise in a dosage of 5,000 units twice a week. After fifteen months of continuous therapy, active spermatozoa were present in small numbers; after twenty months the numbers had not in-

[6] This "course" is considered to be the interrupted therapy given between July and October, 1950. The earlier course was discontinued due to a misunderstanding.

[7] In an unreported case of eunuchoidism-with-low-FSH from this clinic, APL in oil produced definite elevation of 17-ketosteroid excretion in a dosage of 5,000 units a week.

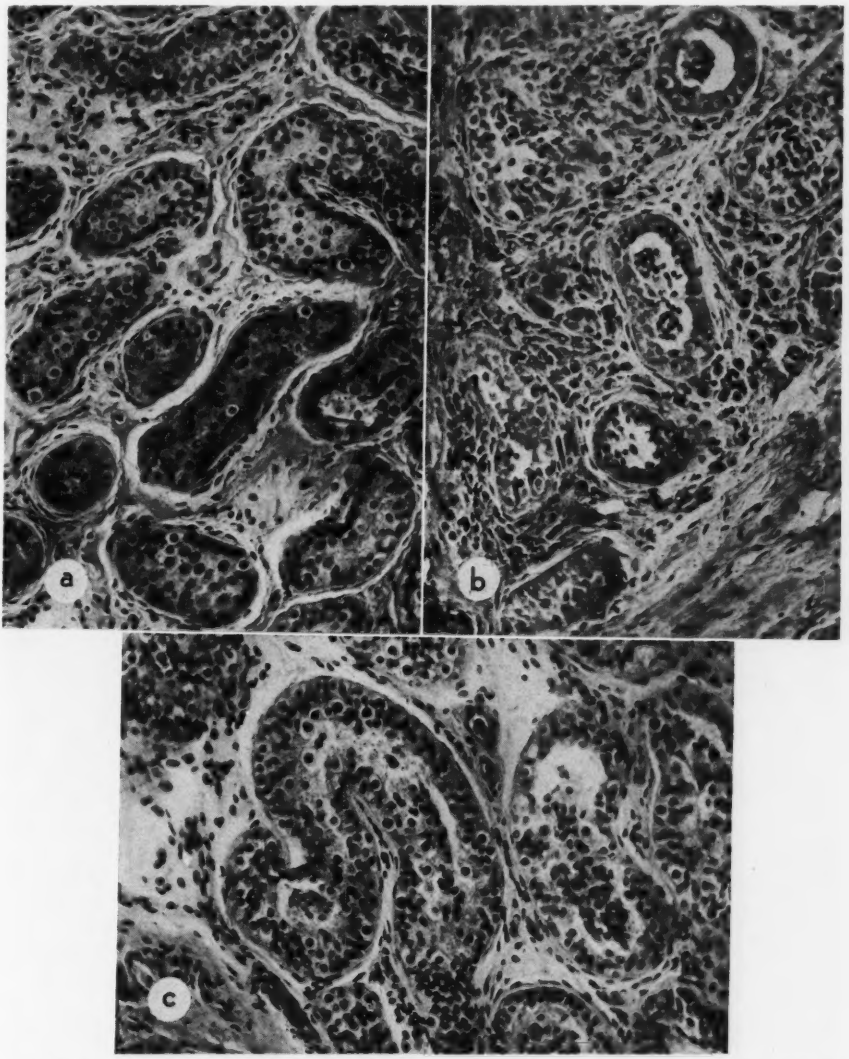


FIG. 11. Photomicrographs of testicular biopsy specimens in Case 2 (×200) (*See* Fig. 3). *a*) Before therapy (Biopsy 1). *b*) After APL in oil (Biopsy 3). *c*) After stopping therapy (Biopsy 4). Note enlargement of Leydig cells in *b*, and regression in *c*.

creased, but the testicular biopsy (Fig. 14) showed almost complete maturation. Addition of methyltestosterone to APL did not increase the numbers of spermatozoa. Following cessation of all therapy, the 17-ketosteroid excretion was as low as it had been when therapy was begun, libido had decreased, and the patient was unable to obtain a semen specimen.

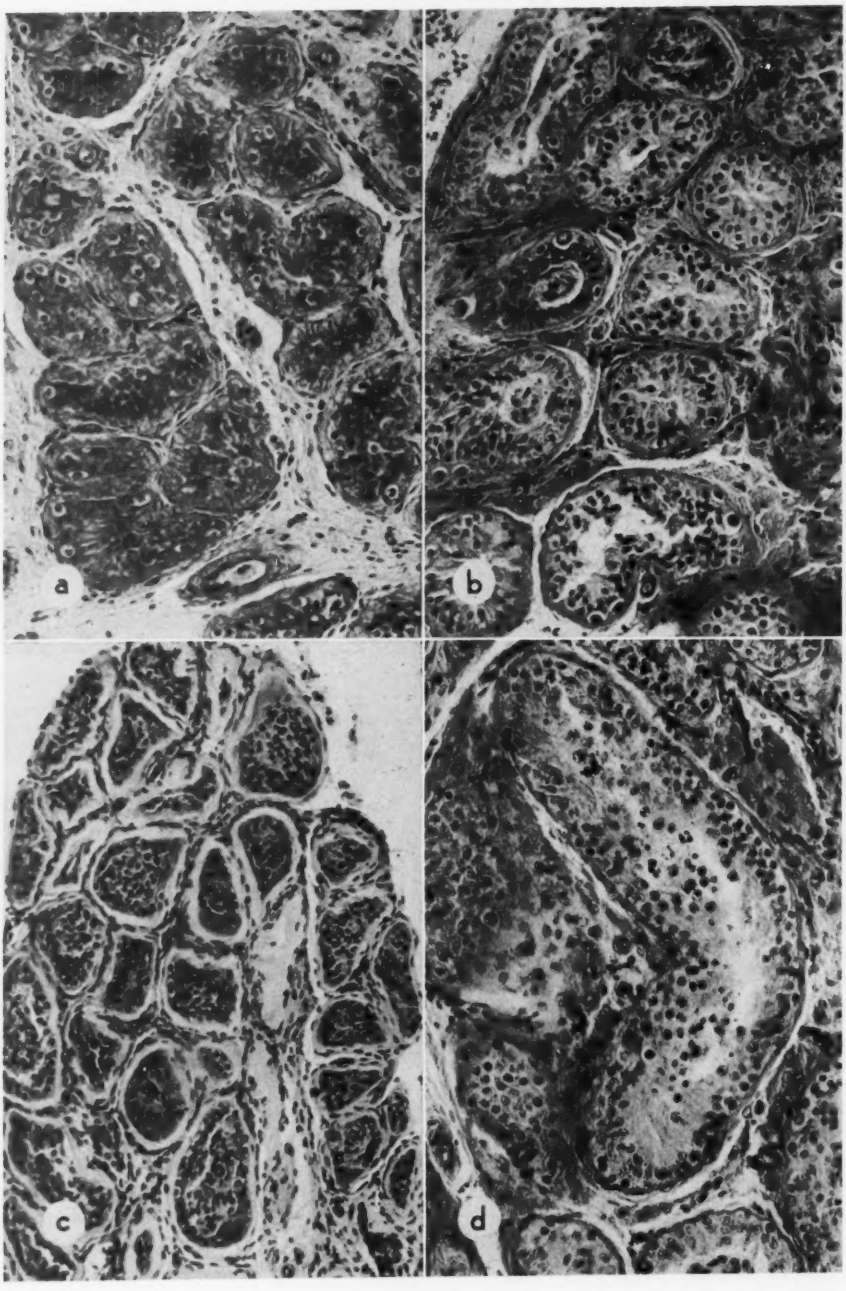


FIG. 12

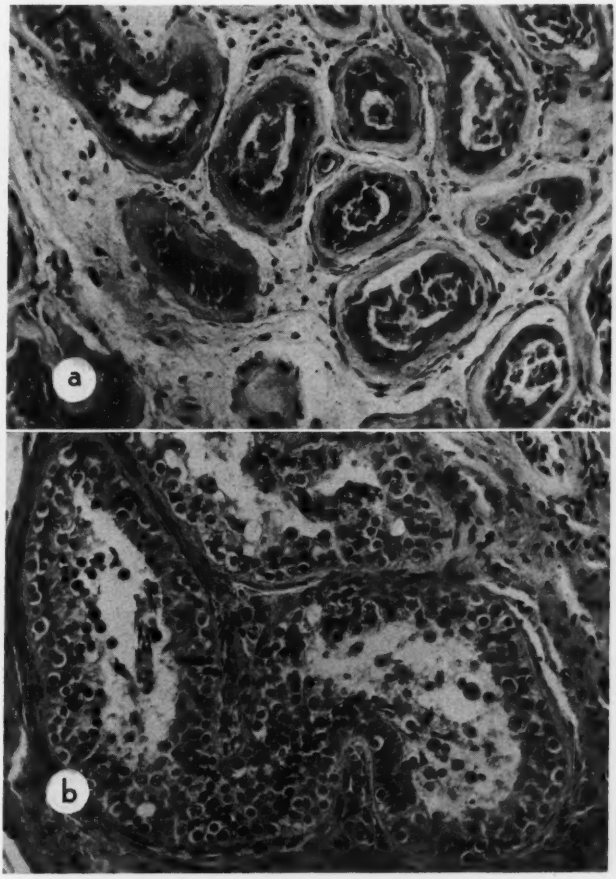


FIG. 13. Photomicrographs of testicular biopsy specimen in Case 6 (×200) (*See* Fig. 7). *a*) Before therapy (Biopsy 1). *b*) After aqueous APL (Biopsy 3). Note especially thinning of tunica propria with therapy.

2. A. L. (Fig. 8) (starting January 1949). APL was administered continuously for a year (in aluminum monostearate, 2,900 units every three days, for two months; in oil, 5,000 units every four days, for three months; in water, 5,000 units every four days, for seven months) and this was supplemented with methyltestosterone (20 mg. a day by linguet) for seven months. The 17-ketosteroid excretion remained high (following the short-term experiment) during APL therapy, except when it was depressed during

FIG. 12. Photomicrographs of testicular biopsy specimens in Case 5 (×200) (*See* Fig. 6). *a*) Before therapy (Biopsy 1). *b*) After aqueous APL (Biopsy 2). *c*) After four months without therapy (Biopsy 3). *d*) After APL in oil (Biopsy 4). Note especially thinning of tunica propria with therapy.

methyltestosterone administration, presumably by depression of adrenal cortical function (8). This therapy resulted in the production of active spermatozoa and a normal testicular pattern (Fig. 15). (The patient's wife became pregnant and a normal child was born on October 31, 1950.)

All therapy was then discontinued, and libido and potentia disappeared; semen could not be obtained, and the 17-ketosteroid excretion fell to pre-treatment levels. Methyltestosterone (20 mg. a day by linguet) promptly restored libido and potentia, but failed to produce spermatozoa over an eight-month period (either alone or in conjunction with

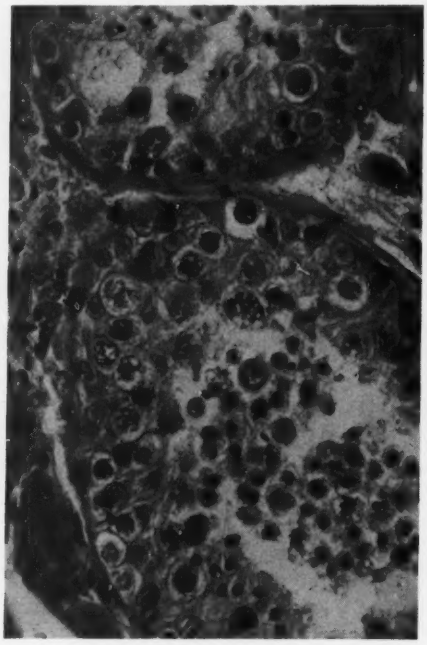
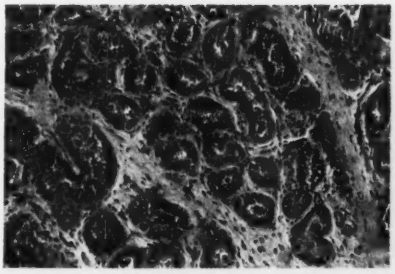


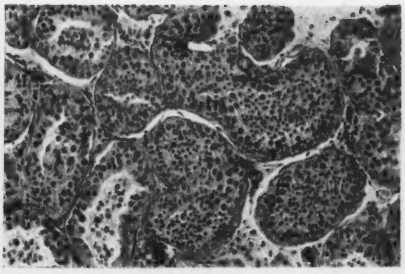
FIG. 15 *d*. Photomicrograph of testicular biopsy specimen, Case 7 (×600). The section is from same field as shown in 15 *c*.

Δ-5 pregnenolone). When APL (water, 5,000 units every four days) was added to the methyltestosterone, active spermatozoa reappeared in three and a half months.

3. F. O. (Fig. 5) (starting April 1948). A two-month course of APL in oil at a dosage higher than that used in the short-term experiment produced no greater effect on the 17-ketosteroid excretion or on the testicular pattern. Normal spermatozoa counts and normal testicular biopsy findings were obtained after twenty months of therapy with methyltestosterone (20 mg. a day by linguet). A course of APL (water) during the methyltestosterone therapy was accompanied by a fall in spermatozoa count (one determination). Twelve months after all therapy was stopped (not shown in the figure) libido, potentia, and spermatozoa count (539,000,000) had remained normal. Urinary FSH had become normal (13 mouse units per twenty-four hours) but the 17-ketosteroid excretion was slightly low (5.8 mg. per twenty-four hours).

14a

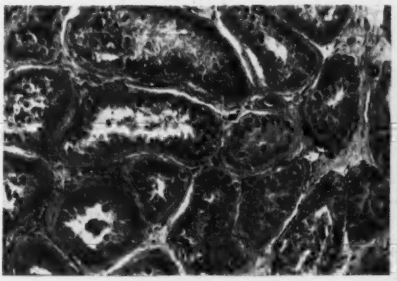


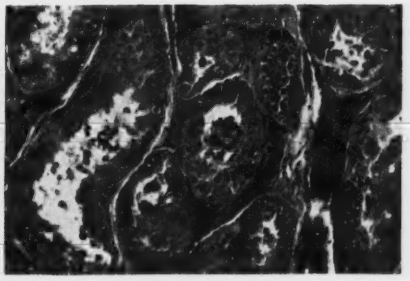


14b

FIG. 14. Photomicrographs of testicular biopsy specimens in Case 3 (×150) (*See* Fig. 4). *a*) Before starting therapy (Biopsy 1). *b*) After twenty-one months of continuous therapy (Biopsy 4). Note presence of spermatozoa in *b*.

15a

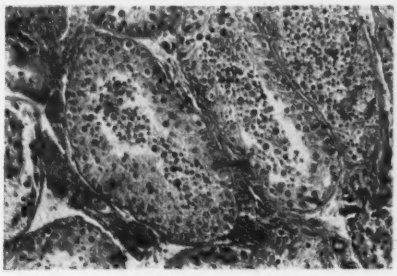




15b

FIG. 15. Photomicrographs of testicular biopsy specimens in Case 7 (×150) (*See* Fig. 8). *a*) Before therapy with APL (Biopsy 1). *b*) After APL in oil (9/48) (Biopsy 2). *c*) After eighteen months of continuous therapy (Biopsy 4).

15c



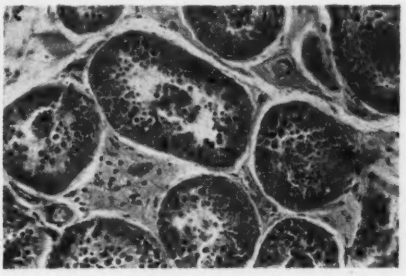


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FIG. 16. Photomicrograph of pre-treatment testicular biopsy specimen (Biopsy 1) in Case 4 (×150) (*See* Fig. 5). Compare with Figures 11a, 12a, 13a and 14a for evidence of maturation before therapy.

DISCUSSION

I. *Diagnosis*

The criteria we have used for the diagnosis of eunuchoidism-with-low-FSH are mentioned in the preceding sections. The syndrome may be confused with panhypopituitarism on the one hand, and with simple delayed puberty on the other. Differentiation from the former is readily made on the basis of 1) a normal rate of growth, 2) 17-ketosteroid excretion higher than that seen in panhypopituitarism, and 3) absence of other evidence of hypopituitarism, *e.g.*, hypoglycemia unresponsiveness, increased insulin sensitivity, history of crises, and evidence of hypothyroidism.

Differentiation of eunuchoidism-with-low-FSH from delayed puberty, which is more difficult, is important in evaluating any given therapy. Thus, if a given therapy initiates puberty, which then proceeds spontaneously, it is impossible to separate the part played by the therapy from that resulting from endogenous hormones. It has been stated (3) that "a surprisingly large proportion of cases of this syndrome maintain their improved status or actually continue to develop towards normal" after therapy with chorionic gonadotropin is withdrawn. To be able to attribute changes to a medication, *e.g.*, APL, one must show regression of the changes after it is stopped. For this reason the mechanism by which spermatogenesis was produced in the cases of Kinsell (9) and of Plum (10) cannot be determined with certainty.

When the present study was terminated, treatment had only very recently been discontinued in Cases 8 and 9, so that the question of regression of APL effects remains open. In Cases 1 through 7, when therapy was stopped the results were interesting. In Case 4 the patient continued to have normal libido and potentia, and normal spermatozoa counts, although 17-ketosteroids remained somewhat low. All the other patients showed decrease of libido and of frequency of erections, loss of potentia with inability to obtain ejaculum for spermatozoa counts, and a fall in 17-ketosteroid excretion. In 2 (Case 5 between courses, Case 2 after therapy) regression of APL effects was demonstrated by biopsy. Thus, from Cases 1, 2, 3, 5, 6, and 7, it may be safely concluded that APL directly stimulated maturation of all elements of the testicular tissue, including the spermatocyte series. In 3 (Cases 3, 6, and 7) spermatozoa were produced. This finding is contrary to the experience of Heller and associates (6), who believe that FSH is required to stimulate spermatogenesis in this syndrome, whereas APL stimulates Leydig cell function alone. Our results are perhaps not surprising, in view of the demonstration by Simpson (11) and by Hamburger (12) in the rat that chorionic gonadotropin has an FSH-like as well as an LH-like action.

An alternative explanation of our findings, namely, that APL acts syner-

gistically with small (often undetectable) amounts of FSH, is not excluded. However, the recent demonstration by Simpson, Li, and Evans (13) that human chorionic gonadotropin by itself will produce spermatogenesis in the immature hypophysectomized rat lends credibility to the former hypothesis.

It was of great interest to see how Patient F. O., in whom therapy ended in a complete cure, differed from the others, in whom it did not.[8] It was at once apparent that whereas F. O. could not be distinguished clinically from the others, his initial testicular biopsy specimen was unique in this series. Thus, it contained tubules with open lumina, mature Sertoli cells, a few spermatocytes, rare spermatids, and even a very rare spermatozoon (Fig. 16).

Hurxthal, Bruns, and Musulin (14) described the appearance of spermatogenesis with chorionic gonadotropin, and its persistence when therapy was stopped, in 2 patients with eunuchoidism. (In one the FSH was shown only not to be elevated; in the other it was "unsatisfactory.") This result suggests that their patients resembled the patient in our Case 4. The published photomicrograph (their Fig. 5) of the pre-treatment testicular biopsy specimen in one of their patients lends striking support to this conjecture: it is like that of F. O. (Fig. 16) and unlike that of the others (Figs. 11–15).

In view of the foregoing considerations, we suggest that male patients with eunuchoidism and low FSH (excluding cases of panhypopituitarism) may fall into one of three categories[9] as follows:

1. *Delayed puberty.* These patients show initially complete immaturity in the testicular biopsy specimen. They respond to chorionic gonadotropin by progressing towards maturation, but when therapy is stopped, the individual patient may or may not continue to mature autonomously. If he does (*e.g.*, those patients reported by Heller and Nelson in whom development continued "off" therapy) it is clearly impossible to ascertain the part played by the therapy. If he does not, one has no assurance that he might not do so following a subsequent course of therapy. It is apparent that this category can be *established* only when the patient "escapes" from it.

2. *Eunuchoidism-with-low-FSH and some testicular maturation (biopsy)* (*e.g.*, our Case 4 and Hurxthal's case). These patients respond to chorionic

[8] The use of relatively more testosterone than APL in this patient does not account for the difference. *See*, for example, initial biopsy findings on Cases 5 and 7, who had received protracted therapy with testosterone before this study.

[9] If one excludes the findings of "eunuchoid proportions" (span greater than height), the normal prepubertal state constitutes a fourth category. Indeed, the decision as to the minimal age at which delayed puberty may be diagnosed remains an arbitrary one. Only in the case of category 2 in the following section is there objective evidence, apart from that of body measurements, of a change from the normal prepubertal state.

gonadotropin by progressing towards maturation, but when therapy is stopped, they continue to mature spontaneously. It is apparent that this category is distinguished from category 1 only by the histologic appearance of the testis.

It is possible that a careful analysis of the initial testicular biopsies in cases thought to represent "cured" eunuchoidism, will place more of them in this group and thus establish a valuable prognostic tool. In our single case in category 2 the FSH returned to normal.

3. *Eunuchoidism-with-low-FSH and complete testicular immaturity (biopsy)* (*e.g.*, our Cases 1, 2, 3, 5, 6, and 7). These patients respond to chorionic gonadotropin by progressing towards maturation, but when therapy is stopped, the changes regress. It is apparent that cases in category 3 will be indistinguishable from those cases in category 1 in which changes initiated by chorionic gonadotropin are not maintained "off" therapy. In this group, effects of therapy can be assessed objectively.

II. *Tunica propria*

In 5 patients (Cases 1, 3, 5, 6, and 7) thickening of the tunica propria was noted in two or more of the testicular biopsy specimens. This finding has been thought (2) to represent a degenerative change, as it is often found when normal gonadal activity has been decreased as a result of disease. This interpretation may apply to Cases 1, 5, and 7, as these patients had all received therapy before this study (*see* Table 2). In Cases 3 and 6, however, the patients had not received any therapy and showed no evidence of previous testicular activity. Of considerable interest is the decrease in the thickness of the tunica which occurred with treatment in Cases 3, 5, 6, and 7, This is clearly shown in Figures 12 and 13. Thickening of the tunica propria has been reported (6) to occur during testosterone treatment in "androgenically normal" males; and to regress upon stopping testosterone therapy.

SUMMARY AND CONCLUSIONS

1. The effects of chorionic gonadotropin (APL) in water were compared with those of APL in oil and beeswax in studies on 9 male eunuchoids with low FSH. Criteria of effects of treatment were 17-ketosteroid excretion and testicular histologic pattern.

It was concluded that the effects of APL in water given at short intervals may be achieved by the use of APL in oil and beeswax given at longer intervals. The data suggest, however, that the aqueous APL may also be effective at the longer intervals.

2. Therapy with APL was prolonged in 2 cases, with the production of mature testes and active spermatozoa, which disappeared when APL was stopped. The wife of one of these patients became pregnant.

3. Prolonged therapy with testosterone was given following APL therapy in 1 case, with concomitant development of mature testes and normal numbers of active spermatozoa, which persisted when testosterone was stopped. The initial testicular biopsy in this patient showed considerable maturation.

4. It is emphasized that effects of treatment cannot be evaluated unless they regress when treatment is stopped. Only on this basis may the contribution of endogenous gonadotropins be ruled out.

5. The data indicate that APL stimulates all elements of the testis.

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THE EXCRETION OF 17-KETOSTEROIDS
II. VALUES IN SEVERAL ENDOCRINE DISTURBANCES

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FOR the estimation of urinary 17-ketosteroids a relatively simple laboratory method is available (1), for which some normal values have been previously recorded (2). Since most, if not all, of these products are believed to be metabolites of androgenic hormones presumably elaborated only by the adrenal cortex and the gonad, their daily excretion in urine, compared with that of normal subjects in relation to sex and age, may reflect in some measure the functional status of the adrenal cortex. High values suggest hyperfunction and low values hypofunction. It is our purpose to present the values for urinary 17-ketosteroids which were obtained in a series of patients, each one of whom had an endocrine disorder.

MATERIALS AND METHODS

All the subjects studied were patients on the wards of the New York Medical College, Metropolitan Hospital Research Unit, and the Flower and Fifth Avenue Hospitals, who were suffering from one of a variety of endocrine conditions.

Twenty-four-hour volumes of urine were collected from each patient on one or more occasions. In subjects with thyroid disease the urine was continuously collected during the entire period of observation and pooled into three-day aliquots for analysis. All results, including those of the pooled aliquots, were averaged and reported as the excretion of 17-ketosteroids in milligram-equivalents of dehydroisoandrosterone per twenty-four hours.

RESULTS AND COMMENTS

I. *Thyroid disease*

There was always a marked depression of the 24-hour excretion of urinary 17-ketosteroids, determined at periodic intervals, in 7 cases of myxedema observed over a period of several months (Table 1 and Fig. 1). The 6 women in this group showed individual averages of 0.6, 1, 2, 2, 2 and 3

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mg. per day, respectively. In the 39-year-old man, a low average value of 9 mg. was obtained. Similarly, low values have been observed by other workers (3–7) who have recorded daily excretions under 3 mg. in almost all of their many cases of myxedema occurring in women, and an excretion of 6.7 mg. in the only case reported by them in a man. Of our subjects, 5

TABLE 1. THE EXCRETION OF 17-KETOSTEROIDS IN PATIENTS WITH HYPOTHYROIDISM, BEFORE AND AFTER TREATMENT WITH DESICCATED THYROID

Age (yrs.)	Before treatment			After treatment			Comment
	BMR %	Tot. serum cholesterol (mg. %)	17-KS (mg./24 hrs.)	BMR %	Tot. serum cholesterol (mg. %)	17-KS (mg./24 hrs.)	
			With myxedema—Females				
23	−25		2				Associated hypo-ovarianism.
33		442	0.6		300	2.5	Cretin. Flat glucose tolerance curve. BMR unobtainable because patient unable to cooperate.
58	−24	310	3	− 8	206	5	Post-thyroidectomy.
60	−33		1	− 9		1	Atrophic thyroid. Poor clinical response to thyroid therapy although BMR rose.
67	−31	257	2	−10	204	4	Atrophic thyroid.
70	−33	465	2	− 9	286	3	Atrophic thyroid.
			Males				
39	−25	325	9				
			Without myxedema—Males				
22	−21		20				Flat glucose tolerance curve.
31	− 8		15				
37	−16		28				
45	−12		13				
56	−25		20				
57	−18	362	10				Flat glucose tolerance curve.

of the women were observed before and during treatment with thyroid hormone. One of these was a 33-year-old cretin who had been without medical supervision for seven years prior to her admission to the hospital. Her average excretion of 17-ketosteroids for several weeks before treatment (0.6 mg. per twenty-four hours) was the lowest figure that we have obtained in any adult, irrespective of the clinical condition present. Following the daily administration of thyroid hormone for three months, this patient showed moderate clinical improvement and an increase in the daily excretion of 17-ketosteroids to 2.5 mg. per twenty-four hours. In 3 elderly

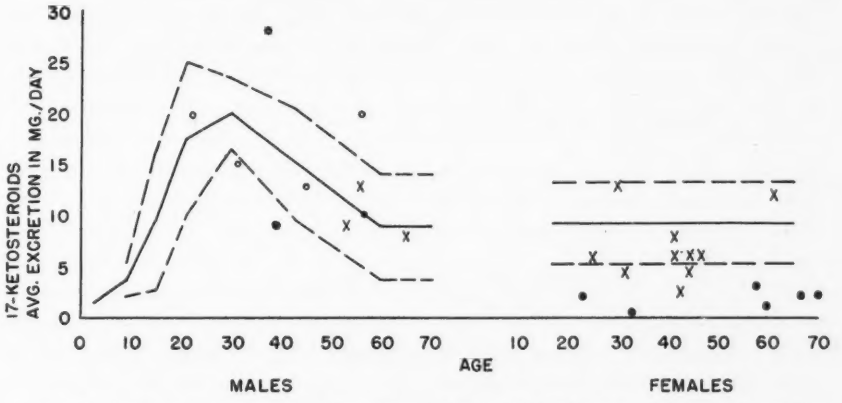

FIG. 1. Average excretion of 17-ketosteroids in individual cases of 1) hypothyroidism with myxedema (•), 2) hypothyroidism without myxedema (o), and 3) hyperthyroidism (x). The values are plotted on a graph which shows the average and range of 17-ketosteroid excretion of normal individuals with relation to age and sex.

patients specific therapy with thyroid hormone did not materially alter the excretion of 17-ketosteroids, although the clinical response, including normalization of the basal metabolic rate and blood cholesterol level, was complete in two. The failure of replacement therapy with desiccated thyroid to restore the excretion of steroids to normal has been observed by others (5, 8) but has not as yet been explained.

In all of 6 cases of hypothyroidism without myxedema, values for 17-ketosteroids in, or slightly above, the normal range were obtained (Table 1 and Fig. 1). These patients were men from 22 to 57 years of age, in whom the diagnosis was established by a) the clinical picture—initial complaint of fatigue, tendency to dry skin and little perspiration, poor tolerance to cold, usually constipation and occasionally bradycardia, b) one or more confirmatory results of laboratory tests, and c) a good clinical response to thyroid therapy. Other possible diagnoses, such as the male climacterium,

TABLE 2. THE EXCRETION OF 17-KETOSTEROIDS IN PATIENTS WITH HYPERTHYROIDISM, BEFORE AND AFTER TREATMENT WITH A THIOURACIL DERIVATIVE

Age (yrs.)	Significant clinical features	Before treatment			After treatment		
		BMR %	Tot. serum cholesterol (mg. %)	17-KS (mg./24 hrs.)	BMR %	Tot. serum cholesterol (mg. %)	17-KS (mg./24 hrs.)
		Females					
25	Slight nervousness and diffusely enlarged thyroid for 2 months. No weight loss. "Compensated" (§)	+55	194	6	+ 4	248	8.5
30	Emotional lability, diarrhea. Nodular thyroid. Normal glucose tolerance curve. "Compensated" (§).	+36	170	13	− 3		12
31	Increasing nervousness and enlarged nodular thyroid for many years.	+40	175	5			
41	Considerable weight loss. Good appetite. Soft palpable thyroid.	+81	162	6	+ 8	220	11
41	Long history of diffusely enlarged thyroid. Marked emotional factors. Diabetic glucose tolerance curve.	+60	150	8	+16	244	10
42	Associated hypo-ovarianism.	+33	300	2.5			
44	Marked weight loss. Recent severe diabetes mellitus. Markedly "decompensated" (§).	+90	120	5	+20	180	9
44	Enlarged thyroid for 15 years. Nervousness for 5 years. Good appetite, moderate weight loss.	+33	100	6	−11		7
46	Nervousness for 4 mos. Diffusely enlarged thyroid. "Compensated" (§).	+88	184	6	+20	264	9
61	Gradual moderate weight loss. Diarrhea for 2 years. Diabetic glucose tolerance curve.	+50	190	12	+ 8	260	11

Males

53	Diabetic glucose tolerance curve.	+42	130	9			
56	Thyroidectomy 22 yrs. previously. Recurrent multinodular goiter.	+33		13			
65	Normal glucose tolerance curve.	+68	165	8			

(§)—"Compensated" and "decompensated" as defined by McGavack (10).

chronic infection and adrenal insufficiency were carefully excluded in these cases. The basal metabolic rate in each instance was moderately low and ranged from −8 to −25 per cent.

Less striking, but nevertheless significant changes in the excretion of 17-ketosteroids were noted in hyperthyroidism (Table 2). Before treatment the figures for the individual averages in 13 cases (10 women and 3 men) were generally below or on the low side of the normal range in relation to sex and age (Fig. 1). Three of the subjects showed values slightly above the normal mean for sex and age, but none showed results above the normal range. No significant correlation was noted between the clinical data, such as severity and duration of the thyrotoxic state, and levels for urinary 17-ketosteroids. However, 3 women with the highest basal metabolic rates (+90, +88 and +81 per cent, respectively) had average urinary excretions of 17-ketosteroids per day which were among the lowest for the group (5, 6 and 6 mg., respectively). The lowest value, 2.5 mg. per day, was obtained in a case of mild hyperthyroidism with associated hypoovarianism and a basal metabolic rate of only +33 per cent.

Low yields have been seen repeatedly in hyperthyroidism (3, 5, 7, 9) but very little attention has been paid to the point that there is no correlation between these values and the clinical findings or the degree of toxicity. The hyperthyroid state, being related to stress, might at first be expected to cause adrenal hyperfunction; prolongation of this state should subsequently lead to exhaustion. In line with this view, McGavack (10) has previously postulated a "compensated" stage of hyperthyroidism characterized by little impairment of general health, good appetite, well maintained weight and, presumably, adrenal hyperfunction; also a "decompensated" stage characterized by impairment of general health, extreme anorexia, weight loss and a decrease in the overactivity of the adrenal cortex. In terms of our laboratory data, using urinary 17-ketosteroids as a measure of adrenal function, the first phase should yield high values and the second, low. Although we considered only the most typical examples of each group we were unable to establish any such correlation (Table 2). Rather,

untreated cases showed moderately low values, regardless of the stage. In the 8 medically treated cases, urinary 17-ketosteroids, determined as the basal metabolic rates approached normal, showed a satisfactory rise when pretreatment excretion had been low, and little change when pretreatment excretion had been normal.

II. *Adrenal disease*

Of 8 patients with Cushing's syndrome 2 were males, 7 and 48 years old, respectively; and 6 were females, from 21 to 44 years of age. All were obese and showed varying degrees of hirsutism. The red cell count was 5 million or above in each case, but hypertension was present in only 4. Abdominal striae were noted in 5 instances, and were pigmented in only 1 of these. As far as could be ascertained clinically, 6 of the cases represented instances of Cushing's syndrome on a basis of primary adrenal hyperplasia. Of these, laboratory confirmation by a positive result from a salt tolerance test was obtained in 2 subjects, and by operative disclosure of an hypertrophied left adrenal gland in a third, who had previously had a negative result from a salt tolerance test. The daily excretions of 17-ketosteroids in these 6 cases were all above the normal range (400, 300, 250, 185, 160 and 155 per cent, respectively, of the mean values shown in Figure 1). In one of the remaining patients the value for 17-ketosteroids was in the normal range; others have suggested that this may indicate an adenomatous lesion of the adrenal cortex (11). In the other remaining patient, a woman with values above 50 mg. per twenty-four hours, a carcinoma was demonstrated. In an excellent review of the subject, Forbes and Albright (11) have classified cases of Cushing's syndrome into three groups, according to the adrenal pathologic changes, and have reported values of urinary 17-ketosteroids that were moderately high in subjects without tumor, low normal in subjects with benign tumor and extremely high in subjects with malignant tumor.

Of 2 cases with an established diagnosis of adrenogenital syndrome, one was in a 10-year-old boy with obesity and some evidence of feminization. His daily average excretion of 17-ketosteroids was 12.4 mg. The other was a girl, 17 years of age, with a masculine type of body build and hirsutism, whose daily urinary excretion of 17-ketosteroids averaged 15 mg. Invariably in this syndrome, values in relation to age have been considerably elevated. In contrast to the low yield found in Cushing's syndrome associated with benign tumor, extremely high values have been encountered in cases with adrenal virilism associated with adrenal adenoma (12).

III. *Male hypogonadism*

The male climacterium is a primary failure of the testes, occurring in the adult and involving metabolic rather than gametogenic function. It

appears clinically with varied symptomatology which may involve any or all of the systems of the body, but is associated with a paucity of significant physical findings.

In our study strict criteria were used (13) in the selection of cases which have been included as climacteric. In these, subjective complaints fell into well recognized patterns, most of which could be classified as general, emotional, neuromuscular, vasomotor, cardiovascular, gastro-intestinal and urinary. The findings on physical examination were essentially negative in each case. Routine laboratory procedures for each subject included an urinalysis, a complete blood count, a Wassermann test, a basal metabolic rate, a roentgenographic examination of the chest, a sedimentation rate and, when indicated, a serum cholesterol determination, a glucose tolerance test and an agglutination test. With few exceptions, no abnormal findings were obtained from the use of any of these procedures. Response to testosterone, a simple therapeutic test, was definite and at times dramatic. As deemed necessary, placebos were used to eliminate possible psycho-therapeutic influences.

Of 413 cases, in relation to age, urinary 17-ketosteroids were below normal in 168, within the normal range in 179, and above normal in 66. Thus, only 40 per cent of our subjects showed some decrease in the excretion of 17-ketosteroids, a finding in general agreement with the work of Werner (14) and an indication of the lack of value of the determination of urinary 17-ketosteroids in the diagnosis of the male climacterium.

Castrates and individuals with complete bilateral atrophy of the testes are examples of primary hypogonadism associated with complete cessation of both gametogenic and endocrine functions of the testes. In such subjects, the sole origin of urinary 17-ketosteroids is presumably from precursors in the adrenal cortex. In 4 males devoid of functioning testicular tissue, aged 19, 33, 47 and 48, values for the urinary 17-ketosteroids corresponded to those in the normal range for women and were 8, 9, 10 and 10 mg. per twenty-four hours, respectively. By contrast, in 20 men with "psychogenic impotence," normal values were always obtained (15).

In connection with the long-term administration of testosterone propionate to 2 agonadal, 2 acromegalic and 5 "normally aging" subjects, we have observed an early marked increase in the urinary excretion of 17-ketosteroids, followed by a decrease to moderately elevated levels while the dosage of drug is maintained. In Figure 2 this point is nicely illustrated, as is also the augmentation of 17-ketosteroid excretion as a result of fever. The latter has been given considerable attention by Forbes and co-workers (9).

IV. *Miscellaneous diseases*

In confirmation of previous reports (3, 4, 6, 16), 3 men aged 19, 24 and

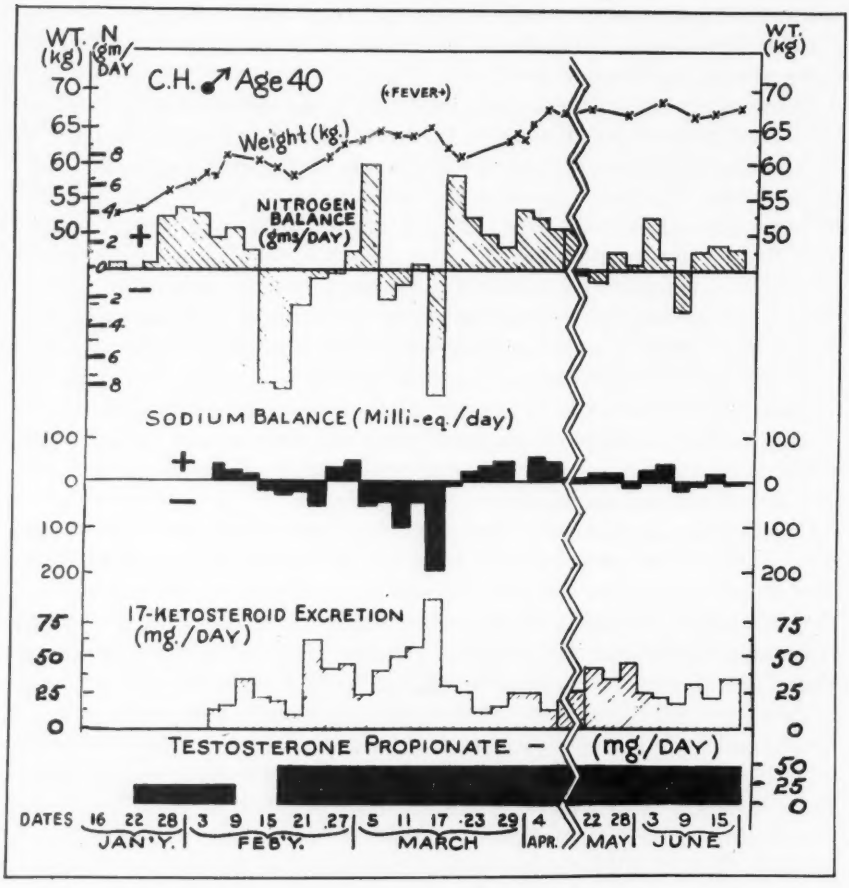
WT. (kg)
N (gm/DAY)
C.H. ♂ Age 40
(+FEVER+)
Weight (kg.)
NITROGEN BALANCE (gms/DAY)
SODIUM BALANCE (Milli-eq./day)
17-KETOSTEROID EXCRETION (mg./DAY)
TESTOSTERONE PROPIONATE — (mg./DAY)
DATES 16 22 28 | 3 9 15 21 27 | 5 11 17 23 29 | 4 | 22 28 | 3 9 15
JAN'Y. FEB'Y. MARCH APR. MAY JUNE

FIG. 2. Early marked increase in excretion of 17-ketosteroids, followed by a decrease to moderately elevated levels, during therapy with testosterone propionate. The augmentation of 17-ketosteroid excretion as a result of fever is also shown.

48 and a girl aged 13, each with a diagnosis of panhypopituitarism, showed extremely low values for urinary 17-ketosteroids, namely, 4.6, 7.0, 5.0 and 2.4 mg. per twenty-four hours, respectively.

A 25-year-old girl with arrhenoblastoma excreted an average of 30.9 mg. of 17-ketosteroids daily in the nine days immediately preceding operation. The lack of precise pathologic definition may account for the variable figures recorded for this condition by Engstrom in his review of reported cases (8).

In accord with the findings of others (3, 7, 17, 18), in 6 men, 38 to 54

years of age, with advanced cirrhosis of the liver, the excretion of urinary 17-ketosteroids was depressed; the average values based on several determinations were 7.0, 6.3, 4.2, 3.5, 3.0 and 2.3 milligrams, respectively. The administration of testosterone propionate, 25 milligrams daily, increased this excretion very slightly,—in sharp contrast to the marked rise seen in hypogonadism (19, 20, 21) or in panhypopituitarism (4, 16).

SUMMARY

1. Values for urinary 17-ketosteroids, estimated by a previously described method, have been determined in several endocrine disorders. The highest levels were observed in a case of adrenal cortical carcinoma and in subjects receiving treatment with testosterone propionate. Values were moderately elevated in the adrenogenital syndrome and in Cushing's syndrome, generally low normal in untreated hyperthyroidism and in male hypogonadism, and low in hypothyroidism with myxedema, in hypopituitarism and in advanced cirrhosis of the liver.

2. In cases of hypothyroidism without myxedema, excretion was within the normal range.

3. Males with bilateral atrophy of the testes showed values corresponding to those in the normal range for women.

4. A subject with arrhenoblastoma of the ovary excreted excessive amounts of 17-ketosteroids.

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GRAVES' DISEASE: HYPERTHYROIDISM OR HYPERPITUITARISM?*†

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THIS report presents the results of an effort to test two theories concerning the pathogenesis of hyperthyroidism. One is the possibility that the disorder is in effect a reflection of hyperpituitarism, the other that it is a derangement apart from the pituitary.

The thyroid in health is thought to alter its level of activity in response to variations in thyrotropin release from the anterior pituitary. An increase in thyrotropin output initiates an outpouring of thyroid hormone into the blood. This in turn acts to suppress the secretion of thyrotropin by the pituitary and, correspondingly, thyroid activity is diminished. A self-regulating system is thus postulated in which the pituitary has a similar role to that of a thermostat. The pituitary-thyroid relationship, in other words, is thought to be a form of servo or feed-back mechanism (1).

If the foregoing assumption is correct, then Graves' disease or hyperactivity of the thyroid could as well be the result of a derangement of the pituitary portion of this mechanism as of the thyroid part. This normal interrelationship between the two glands is schematically presented in Figure 1. Possible intermediate steps, such as thyroid hormone affecting the hypothalamus and thus the pituitary, have been omitted. Two possible mechanisms are indicated in Figure 1 by which hyperthyroidism might originate as the consequence of a derangement in pituitary function. In one, the anterior pituitary is shown in the role of a "thermostat" set too high, maintaining an abnormally elevated blood level of thyroid hormone, but normally rseponsive to variation from this level. In the other, a lack of pituitary responsiveness to thyroid hormone is shown as the cause of hyperthyroidism, The pituitary is considered as no longer responding to increases in thyroid hormone blood level by a compensatory decrease in thyrotropin output. Similar unresponsiveness, which would be only apparent, might result from an abnormal secretion by the thyroid which would be incapable of inhibiting thyrotropin release.

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If either of the above mechanisms was truly responsible for Graves' disease, certain consequences should ensue. Assuming the first mechanism to be correct, that the pituitary is set to maintain an abnormally high thyroid blood hormone level, there would exist by definition a marked endogenous thyrotropin excess to produce the hyperactivity of the thyroid. The addition of small amounts of thyrotropin relative to the amounts already postulated as being present in this system, by parenteral administration,

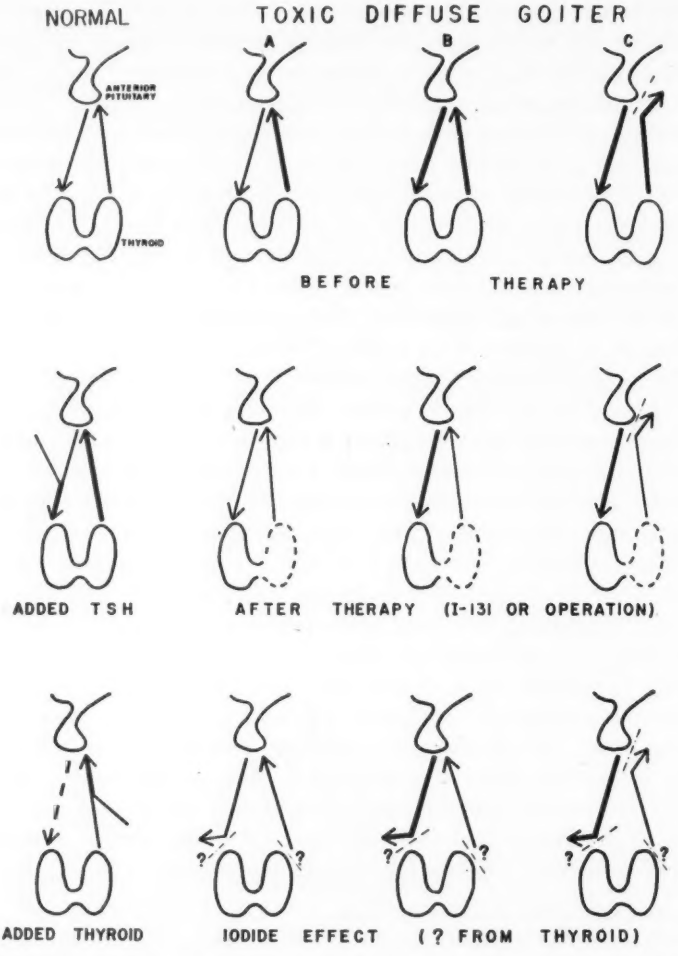

FIG. 1. Schema of postulated normal thyroid-pituitary interrelationship and of possible derangements in disease. TSH is used for "thyrotropin." Iodide effect is represented and the possibility of an iodide effect from administered thyroid is indicated.

should induce little or no response from the already hyperthyroid gland. On the other hand, pituitary activity should be decreased by the administration of exogenous thyroid hormone as in the normal subject, since the pituitary is postulated as reacting to thyroid hormone excess above the elevated equilibrium point.

In the euthyroid state induced by removal of the major portion of the

CATEGORY	DIRECTION† OF RESPONSE							
	BEFORE RADIOIODINE THERAPY				AFTER RADIOIODINE THERAPY			
	TSH		THYROID		TSH		THYROID	
	RAI	SPI	RAI	SPI	RAI	SPI	RAI	SPI
EXPERIMENTAL RESULTS	→	↑	↑OR →	↑	↑OR →	↑	↓	↑
THEORETICAL RESULTS								
INTRINSIC THYROID OR NON-PITUITARY DISORDER (FIG. 1, A)	↑OR →	↑OR →	→	↑OR →	↑OR →	↑OR →	↓	↑OR →
INTRINSIC PITUITARY OR HYPOTHALAMO-PITUITARY DISORDER (FIG. 1, B)	→	→	↓	→	→	→	→	↑
LOSS OF RESPONSITIVITY TO THYROID HORMONE (FIG. 1, C)	→	→	→	↑OR →	→	→	→	↑
EUTHYROID CONTROL RESULTS (FIG. 1, NORMAL)	↑	↑	↓	↑OR →				

† ↑ INCREASE
→ NO CHANGE
↓ DECREASE

FIG. 2. Diagram of results to be expected from the administration of thyrotropin (TSH) and of thyroid in untreated and in I^{131}-treated Graves' disease according to the mechanisms outlined in Figure 1, and a comparison with the results of actual experiment. The arrow pointing up means an increase; down, a decrease; and horizontal, no change (as used by Means, J. H. (*cf.* (5)) p. 169).

gland, as after I^{131} therapy, the responses to administered thyroid and thyrotropin can again be anticipated, provided the basic pathologic mechanisms have not been altered by the therapy. Since there should still exist a marked endogenous thyrotropin excess due to reduction of the level of circulating thyroid hormone below that neeeded to arrest thyrotropin release, exogenous thyrotropin in small doses should produce a negligible

response. The administration of thyroid in low dosage, however, should not cause suppression of the pituitary, as in the hyperthyroid state, so long as hyperthyroid blood levels are not attained.

In the event that the second mechanism is the cause of Graves' disease, a loss of responsiveness of the pituitary to thyroid hormone, other consequences should ensue. Hyperthyroidism would again be the result of en-

TABLE 1. EFFECT OF THYROTROPIN ON I^{131} UPTAKE AND SPI IN TOXIC GOITER, UNTREATED AND IN REMISSION FROM RADIOIODINE THERAPY

Duration of thyrotropin therapy	Thyroid status	No. of patients	Average thyroidal uptake of I^{131} at 24 hrs. (%)			Average SPI (γ%)		
			Before	After	Diff.	Before	After	Diff.
3 days	Toxic	22	59	58*	−0.1 (−21 to +14)	12.5	15.1	+2.6 (+0.1 to +7.0)
	Remission: 6 mos.	14	31	38†	+7† (−18 to +18)	6.0	6.8*	+0.8‡ (−1.8 to +3.7)
	12 mos.	0	—	—	0	—	—	—
	Controls (euthyroid)	7	25	47	+22 (+10 to +44)	6.1	10.4	+4.3 (+1.2 to +8.5)
1 day	Toxic	0	—	—	—	—	—	—
	Remission: 6 mos.	8	28	28	0 (−20 to +14)	5.1	4.6	−0.5 (−2.2 to +0.7)
	12 mos.	9	27	27	0 (− 6 to +14)	5.3	5.7	+0.4 (−1.7 to +3.3)
	Controls (euthyroid)	5	27	38	+11 (+3 to +20)	4.6	6.0	+1.4 (+0.0 to +6.6)

* One patient only with an uptake less than 40 per cent.
† Excludes 1 patient with extreme difference of 61 per cent.
‡ Excludes 1 patient with extreme difference of 11.0 per cent.

dogenous thyrotropin excess. The overstimulated thyroid once more should show a negligible response to small amounts of exogenous thyrotropin but, by definition, there should also be no response to the administration of thyroid hormone. This latter would not hold, if an abnormal thyroid secretion were the cause of the pituitary unresponsiveness.

After euthyroidism induced by I^{131} therapy, according to this theory, endogenous thyrotropin excess should be undiminished and hence there should persist a negligible response to exogenous thyrotropin and an equal failure of response to exogenous thyroid as before, since the primary refractoriness of the pituitary has not been altered; again, a response to thyroid should result, in the event of an abnormality of thyroid secretion.

If hyperthyroidism is not mediated by pituitary hyperfunction, certain different consequences might be postulated. Complete suppression of endogenous thyrotropin release should result from an excess of thyroid hormone in the blood. The administration of exogenous thyrotropin should now evoke a thyroid response since there is no circulating thyrotropin, whereas

TABLE 2. EFFECT OF THYROID MEDICATION ON I^{131} UPTAKE AND SPI IN TOXIC GOITER, UNTREATED AND IN REMISSION FROM RADIOIODINE THERAPY

Duration of thyroid therapy	Thyroid status	No. of patients	Average thyroidal uptake of I^{131} at 24 hrs. (%)			Average SPI (γ%)		
			Before	After	Diff.	Before	After	Diff.
1–2 wks.	Toxic	6	52	57	+5 (−15 to +23)	12.0	12.0	±0 (−1.9 to +2.4)
	Remission	0	—	—	—	—	—	—
	Controls (euthyroid)	5	21	14	−7	6.2	6.2	±0
3–5 wks.	Toxic	6	55	60	+5 (−21 to +18)	11.4	13.0	+1.6 (−2.5 to +3.3)
	Remission: 6 mos.	12	46	35	−11 (−23 to +25)	6.7	8.5	+1.8 (−3.3 to +6.1)
	12 mos.	0	—	—	—	—	—	—
	Controls (euthyroid)	4	21	12	−9 (−20 to ±0)	5.5	5.5	±0.0 (−1.3 to +2.4)
6 wks.	Toxic	5	58	49	−9 (−11 to +14)	12.7	13.1	+0.4 (−2.5 to +3.9)
	Remission: 6 mos.	2	49 & 50	30 & 40	—	10.1 & 6.4	10.0 & 8.9	—
	12 mos.	3	31	11	−20	5.2	6.6	+1.4
	Controls (euthyroid)	2	39 & 44	4 & 1	—	3.9	4.9	—

the addition of thyroid hormone by medication should have little effect upon an already inactive pituitary. By contrast, when euthyroidism has been produced by I^{131} therapy, these responses should be altered. Exogenous thyroid should be effective in suppressing the pituitary, which is again releasing thyrotropin following lowering of the blood hormonal iodine level. The response may be somewhat less than in healthy subjects, since hyperfunction of the residual thyroid tissue probably persists because the basic disorder responsible for hyperthyroidism has presumably not been affected by the I^{131} therapy. In other words, over-all thyroid activity is normal but this may be the result of a small amount of hyperactive residual

tissue. Similarly, the response to exogenous thyrotropin by the hyperactive thyroid remnant should be less than normal because of the reappearance of endogenous thyrotropin with euthyroidism.

The postulated responses to thyrotropin and thyroid just described are illustrated in Figure 2. The actual results of the present studies with thy-

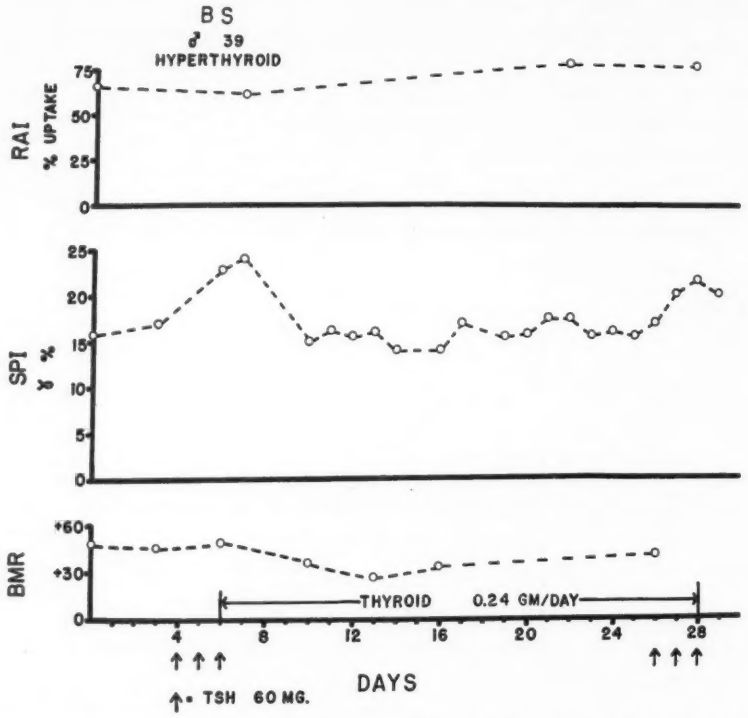

FIG. 3. Illustrating response to thyrotropin (TSH) in active Graves' disease, and lack of response to moderate doses of thyroid.

rotropin and thyroid substance are shown for comparison. Tables 1 and 2 and Figures 3–6 give the data from this study and show the number of observations made, mean values and range of values for the 24-hour uptake of I^{131} measured directly over the thyroid, and the level of serum precipitable iodine, as measures of thyroid activity. These values are shown for the hyperthyroid and euthyroid states following the use of thyrotropin and thyroid, and for healthy control subjects similarly treated. The experimental findings do not fit with those hypotheses which involve hypersecretion of the anterior pituitary in the pathogenesis of Graves' disease. The

responses obtained do correspond with those predicated in the event of a disorder not mediated by the pituitary.

DISCUSSION AND CONCLUSION

The results of this study tend to indicate that Graves' disease is primarily hyperthyroidism and not hyperpituitarism. It is recognized that the

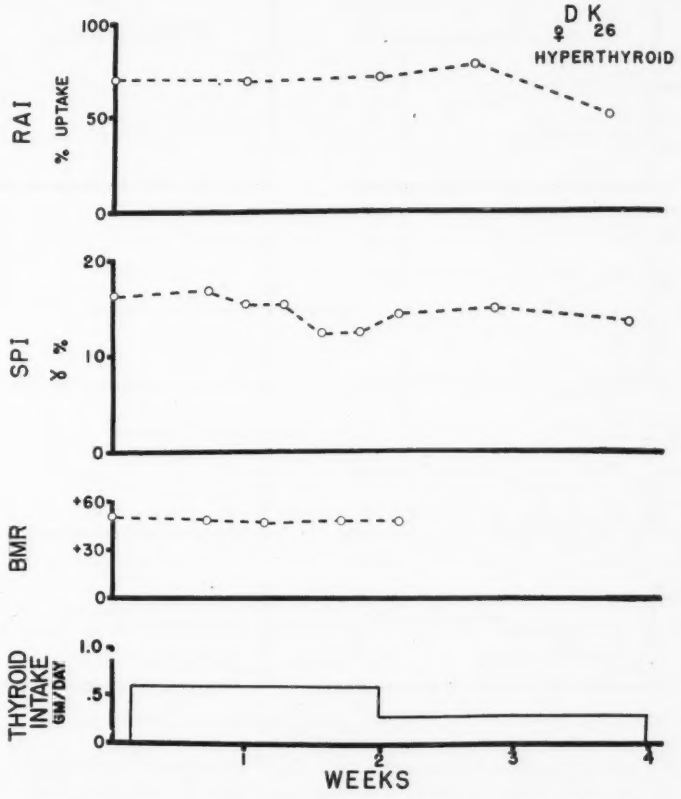

FIG. 4. Showing lack of significant response to large doses of thyroid in active Graves' disease.

evidence is indirect. It is also recognized that the thyroid-pituitary relation as illustrated may be the composite of a series of intermediary steps, and that suprapituitary and suprathyroid control mechanisms may also be involved. Nevertheless, the evidence obtained herein strongly suggests that hyperthyroidism need not necessarily involve those mechanisms which entail pituitary hyperfunction. This would explain the failure of

many workers regularly to detect thyrotropin in the blood of patients with Graves' disease (2), although thyrotropin inactivation by the thyroid could equally well account for this finding (3). The conclusions of the present study also agree with the observation of Astwood (4) that euthyroidism can be induced and maintained by the use of antithyroid drugs in Graves'

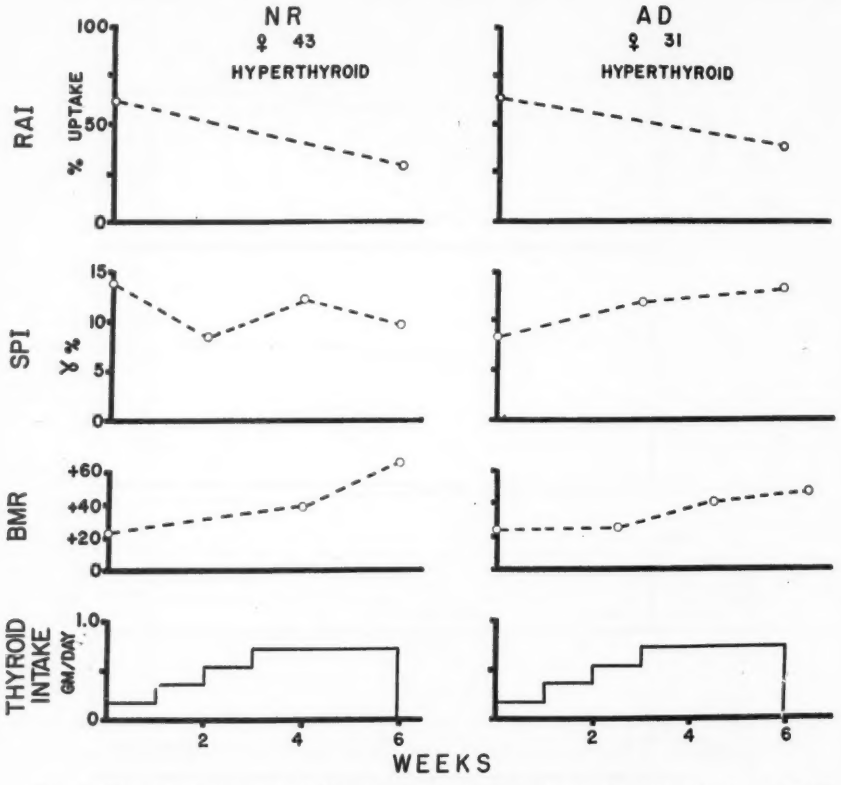

FIG. 5. Showing decrease in 24-hour uptake of I^{131} during oral administration of 0.72 Gm. of thyroid daily, with decrease of serum precipitable iodine level in one instance (N.R.), and increase in the other (A.D.).

disease for long periods of time without thyroid enlargement, whereas rapid enlargement occurs if hypothyroidism is brought about by this therapy. He suggests that the change in thyroid size represents a response to thyrotropin in the circulation.

Means (5) has reported clinical improvement after thyroid medication in Graves' disease. Several of the patients with hyperthyroidism in this study and in one by Greer (6) have shown a limited decrease in I^{131} uptake

or have not revealed an increase in serum hormonal iodine level coincident with the administration of large doses of thyroid substance. Greer, particularly, has suggested that inhibition of pituitary, and hence thyroid, function was achieved. This would account for the failure of the blood level to increase upon the ingestion of desiccated thyroid. However, several nonspecific reasons may equally well explain this apparent response. Desic-

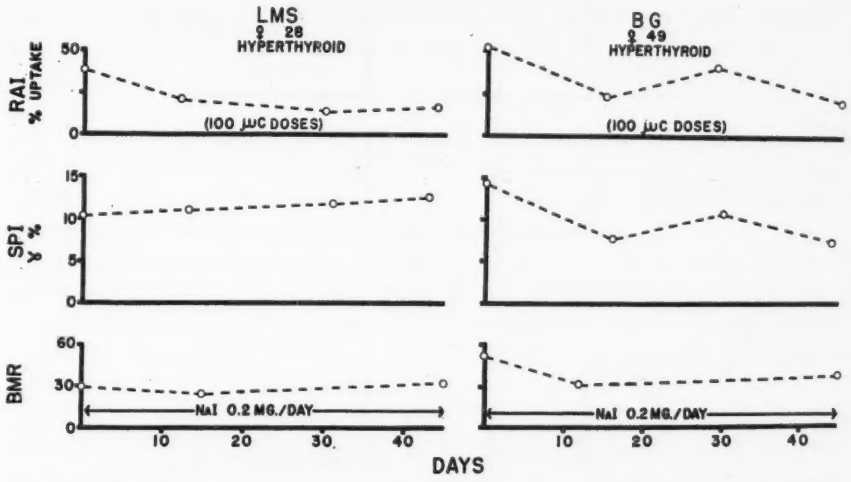

FIG. 6. Showing changes in I^{131} uptake and in serum precipitable iodine level similar to those found during oral administration of thyroid (Fig. 5), using inorganic iodine as sodium iodide and three weekly diagnostic tracer doses of 100 microcuries each (7).

cated thyroid includes fairly sizable amounts of nonhormonal iodine, as well as of hormonal iodine. As much as 2.0 mg. of sodium iodide equivalent may be given daily in 600 to 720 mg. of thyroid powder. This amount of inorganic iodine may induce an iodide effect on the hyperthyroid gland, apart from any suppressive action of the associated thyroid hormone upon the pituitary.

Similarly, marked amelioration of hyperthyroidism, both clinically and in laboratory values, has been found to result from as few as two or three test doses of I^{131} used to follow the course of the hyperthyroidism during the administration of thyroid medication (7). This radiation effect may cause a drop in serum hormonal iodine apart from any use of thyroid. Finally, bed rest and sedation occasionally may cause a considerable decrease in the degree of thyroid hyperfunction. These nonspecific causes, then, for decrease in thyroid activity appear to account staisfactorily for the occasional failure of the serum iodine level to rise when thyroid is ad-

ministered, and for the decrease in I^{131} uptake also seen, without being indicative of pituitary suppression by exogenous thyroid hormone.

Apart from change in thyroid function, the fact that the serum hormonal iodine level did not increase upon thyroid feeding may also possibly be the

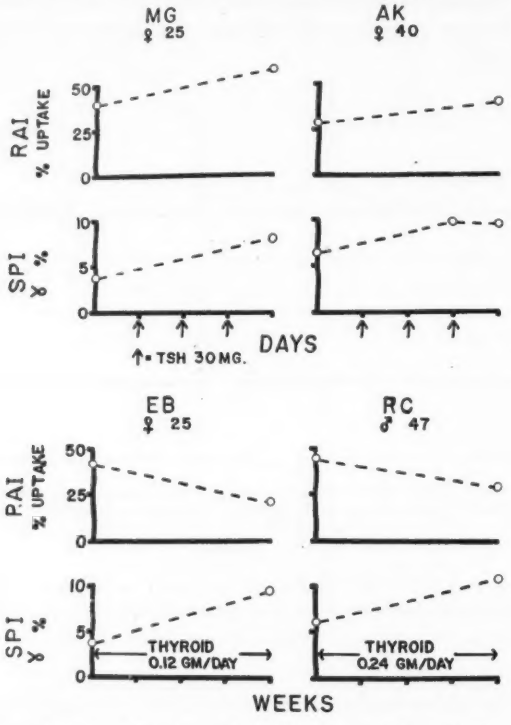

FIG. 7. Showing changes following administration of thyrotropin and thyroid, in radioiodine uptake at twenty-four hours and in the serum precipitable iodine level, in the euthyroid state consequent to I^{131} therapy administered less than six months previously for hyperthyroidism.

result of increased efficiency of normal disposal mechanisms for circulating thyroid hormone, due to the hyperthyroidism.

It should be noted that the responses to thyrotropin and thyroid by the patients in whom euthyroidism has been induced by I^{131} therapy are somewhat less than those shown by the healthy control subjects similarly tested. This suggests that the remnant of thyroid tissue is still hyperactive. The evidence is recognized as being purely circumstantial, in the light of the many unknown alterations which may follow therapeutic intervention. In fact, most of the patients treated with I^{131} a year or more before receiving thyrotropin or thyroid also show the same diminution in response to these

agents compared to healthy subjects. This possibly is evidence that the active hyperthyroid process persists in most patients even beyond a year after euthyroidism has been induced, and tends to suggest that relief of hyperthyroidism may be the consequence of mechanical removal of functioning thyroid tissue and not the result of the interruption of a vicious circle responsible for the disorder. The relatively high recurrence rate which follows operation for Graves' disease might thus be explained. The persistent hyperplasia of the thyroid stump up to five years after subtotal thyroidectomy (8) is also consistent with this view.

SUMMARY

1. Thyrotropin and thyroid have been administered to patients with active, otherwise untreated Graves' disease, and to patients recently brought into a state of remission with I^{131}, to test the hypothesis that hyperthyroidism is the result of hyperpituitarism.

2. Thyrotropin produced an increased release of hormone from the thyroid in active Graves' disease as judged by an increase in the serum precipitable iodine level, whereas thyroid administration did not significantly depress the hyperthyroid gland as judged by the 24-hour uptake of radioiodine.

3. Thyrotropin produced a slight rise in the level of serum precipitable iodine in I^{131}-treated Graves' disease. Thyroid by mouth decreased the 24-hour uptake of I^{131}.

4. These data tend to indicate that hyperthyroidism arises from mechanisms not mediated through the anterior pituitary. The results are discussed.

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SERUM PROTEIN-BOUND IODINE DURING INGESTION OF DESICCATED THYROID*

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IT HAS been demonstrated that hypothalamic-adenohypophyseal regulatory mechanisms maintain the production and release of thyroid hormone within euthyroid limits (1, 2). Previous observations from this laboratory have indicated that without exogenous thyroid or iodide intake the protein-bound iodine in healthy adults remains relatively constant (3). Granting adequate analytic precision, such constancy is compatible with, but does not necessarily support, the existence of a "feed-back" mechanism activated by changes in the plasma level of thyroid products. Introduction of exogenous thyroid products into such a system should provide evidence, however, concerning the presence and the efficiency of such adaptive responses. This report describes the effects of thyroid feeding on serum protein-bound iodine levels and other pertinent indices in euthyroid adult males.

PROCEDURES

Desiccated thyroid of the same lot number[1] was administered in amounts ranging between 1 and 6 grains per day to 9 presumably healthy adults during intervals up to eighteen weeks in length. In addition to serial determinations of circulating serum protein-bound or precipitable iodine (4, 5), frequently on two successive days, approximately one week apart, electrocardiographic tracings, basal metabolic rate, body weight, pulse rate, serum cholesterol (6), and creatine (7) measurements were obtained in a number of the studies. All of the subjects knew that they were receiving desiccated thyroid and were aware of the daily dosage.

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† Damon Runyon Clinical Research Fellow.

[1] Parke, Davis and Company's desiccated thyroid, ½ and 1 grain sizes of lot #J2223C-1, was kindly supplied by Dr. Hervey C. Parke.

RESULTS

In the first group of 4 subjects the results of protein-bound iodine analyses during thyroid ingestion, 3 grains per day, have been compared graphically and statistically with the results in preceding and subsequent periods (Fig. 1). The mean values rose significantly ("*p*" less than 0.05) during thyroid therapy in the first 2 subjects, Ga. and M., but not in the last 2. On the other hand within a few days following cessation of thyroid therapy the average protein-bound iodine value decreased in all 4 experiments to levels below those present in the control observations. The isolated observations on the ninety-fifth and ninety-sixth days in Subjects N. and H. suggest that in the subsequent interval pretreatment concentrations had been restored. It should be further noted that during thyroid

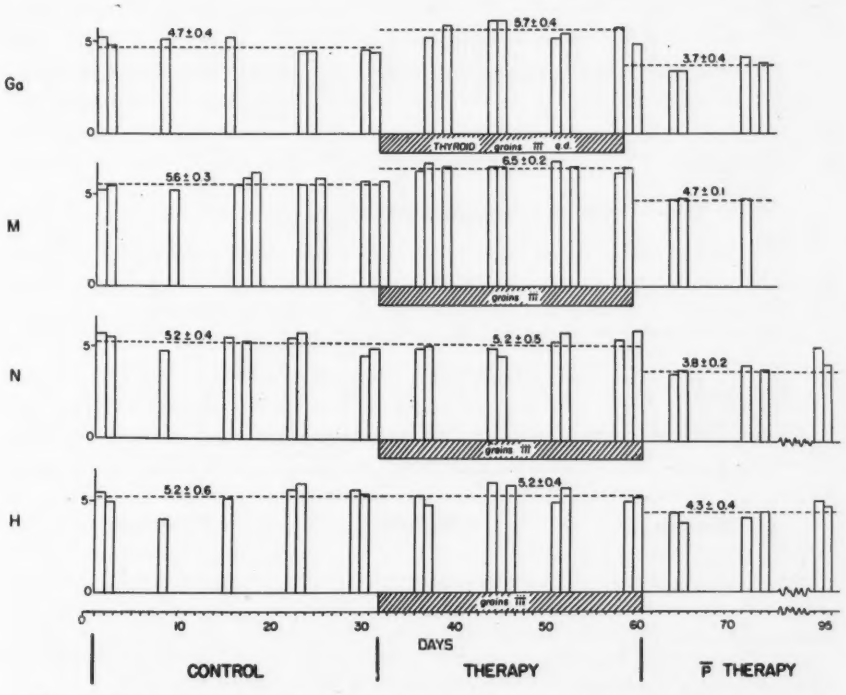

FIG. 1. The daily oral administration of 3 grains of thyroid to euthyroid subjects for approximately one month produced a rise in serum protein-bound iodine levels above those characteristic of the control period, in Ga. and in M., but not in N. or in H. The week-to-week fluctuations were not increased by thyroid therapy in any of the 4 subjects. When the administration of thyroid was discontinued, prompt but reversible decreases of protein-bound iodine values below those in the treatment or pretreatment periods were recorded.

administration the fluctuations in protein-bound iodine concentration from day to day, at least at those times when this fraction was measured, did not exceed the changes recorded in the pretreatment phase. This is clearly evident from the respective mean values and their standard deviations.

In 5 subjects (Fig. 2) an initial intake of 1 grain of thyroid daily was successively increased to a final dosage of 3 or 6 grains per day.

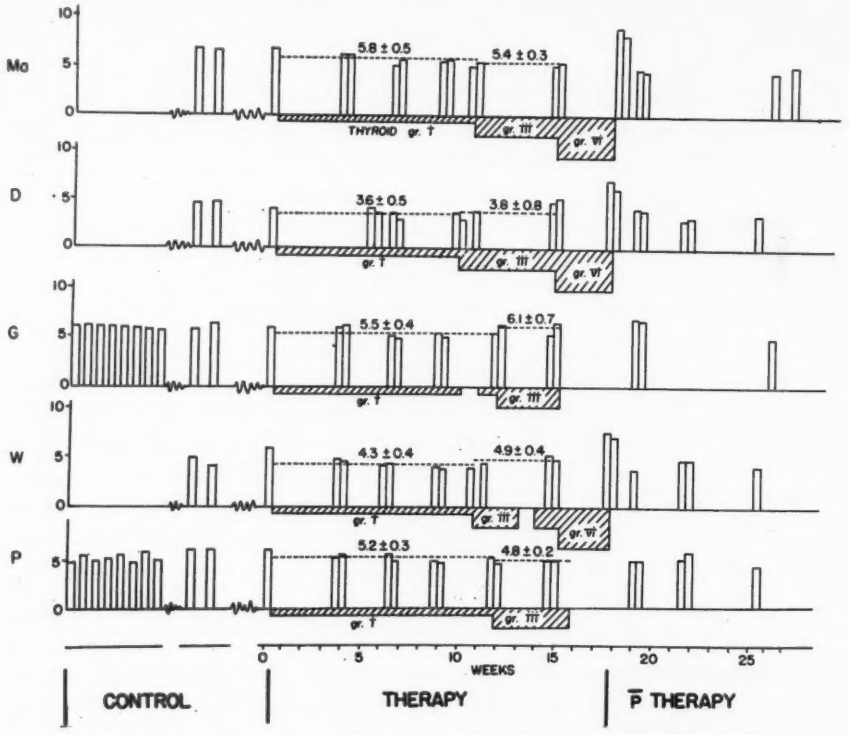

FIG. 2. During ingestion of daily 3-grain supplements of desiccated thyroid the serum protein-bound iodine levels were no higher than those recorded during ingestion of 1 grain. Increasing the intake per day to 6 grains (Subjects Ma., D. and W.), raised the protein-bound iodine concentrations above pretreatment values, as well as above those observed during the ingestion of 1 or of 3 grains of thyroid daily.

Treatment with 3 grains per day did not, during the period of observation, raise the protein-bound iodine values above those present on 1-grain dosage levels nor above those recorded prior to therapy (Fig. 2). During administration of 6 grains per day to 3 subjects (Ma., D., and W.) the protein-bound iodine values rose well above any concentrations noted previously in the same subjects and as a matter of fact approached or exceeded

the upper limit characteristic of the euthyroid adult, reaching levels of 9.0, 7.0, and 7.9 gamma per cent, respectively (8).

The ingestion of 1 grain of desiccated thyroid daily produced no discernible clinical symptoms in any of the subjects. Body weights, pulse rates, and serum cholesterol levels remained unchanged. During ingestion of 3 grains per day, a tachycardia of 112 per minute developed in Subject P. on the twenty-third day of treatment (Fig. 2). This disappeared three days after withdrawal of the drug. Electrocardiograms remained essentially unchanged in this individual, as well as in all others. Increases in the basal metabolic rate, without exceeding the upper limit of normal, were observed in the 3 subjects receiving 6 grains daily. These increases were associated with distinct losses of body weight—2.5 and 4.0 kilograms in D. and in W., respectively. All 3 of these subjects, receiving 6 grains daily of exogenous thyroid (Fig. 2), showed a rise in fasting serum creatine levels (Subject Ma., 0.18 to 0.34; D., 0.19 to 0.47; and W., 0.23 to 0.50 milligrams per cent), without creatinuria (9). Thyroid ingestion, 3 or 6 grains per day, was accompanied by decreases in the serum cholesterol level, ranging between 13 and 59 milligrams per cent. In each instance these were cancelled or exceeded by rises in the post-therapy period.

DISCUSSION

The data presented suggest that in euthyroid individuals the administration of 1 grain of desiccated thyroid per day for as long as twelve weeks does not raise the level of circulating protein-bound iodine when measured at intervals of approximately one week. A daily dosage of 3 grains produced no rise in 7 out of 9 subjects. In the remaining 2 subjects and in all 3 maintained on 6 grains, the protein-bound iodine level did rise. These findings indicate that as much as 3 grains of desiccated thyroid per day can be ingested by some euthyroid subjects without discernible change in the week-to-week stability of the protein-bound iodine level. This constancy cannot be attributed to an insufficient sensitivity of the index employed, since other studies have shown that the concentration of protein-bound iodine can indeed be readily influenced by a variety of clinical and experimental situations (5, 8, 10–12).

Assuming complete absorption, a number of factors may be operative in such an adjustment: a) decreases in the endogenous production and release of thyroxine, b) alterations in the serum binding and transport of the protein-bound or thyroxine iodine irrespective of its exogenous or endogenous source, and c) adjustments in the degradation or excretion of these iodine fractions in the tissues or via organs. Support for the first of these is present in the demonstration that the thyroidal uptake of labelled radioactive iodine decreases markedly or ceases entirely with sufficient amounts of exogenous thyroid (13). This cannot be attributed solely to diminished

thyroid-stimulating hormone effects, since even complete absence of the anterior pituitary results in only a partial suppression of thyroid productivity (14–16). The possible participation of other endocrines and of the adrenal cortex in particular should be cited, since 11-oxygenated steroids do inhibit the thyroid, and adrenal gland size does increase with increases in thyroid activity (17–20). Irrespective of the mediators involved, the importance of thyroid inhibition in the adjustment to exogenous thyroid seems well established. Further support for its existence is present in the post-therapy drop in protein-bound iodine levels observed in our subjects, as well as in others (21), suggesting a lag phenomenon in resuming thyroxine production, akin to that which follows withdrawal of exogenous cortisone therapy in eu- or in hypoadrenalism (22). No data are available as to whether or not the homeostasis may also be related in part to changes in the transport system or in the catabolism or excretion of this iodine fraction.

SUMMARY AND CONCLUSION

1. The serum protein-bound iodine level measured at weekly intervals remained unchanged in 5 euthyroid subjects maintained on 1 grain of desiccated thyroid per day; the same stability was observed in 7 of 9 other studies with 3-grain supplements.

2. Administration of 3 grains of desiccated thyroid to 2 subjects and of 6 grains to 3 others did raise the serum protein-bound iodine level significantly.

3. Fluctuations in day-to-day iodine values were not increased during thyroid therapy.

4. Temporary decreases in serum protein-bound iodine levels below those in the pretreatment period were observed in subjects in whom measurements were made following withdrawal of the 3-grain daily supplement of desiccated thyroid.

5. Regulatory mechanisms exist in euthyroid individuals for the maintenance of constant levels of protein-bound iodine during the administration of limited amounts of desiccated thyroid.

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CHRONIC THYROIDITIS: A CLINICAL AND PATHOLOGIC STUDY OF 354 PATIENTS*†

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CHRONIC thyroiditis, as evidenced by lymphoid infiltration, fibrosis and epithelial alteration of the thyroid gland, is a poorly defined thyroid disorder. Since the classic descriptions of Riedel (1, 2, 3) and Hashimoto (4), numerous controversial reports on chronic thyroiditis have appeared in the literature (5–24). These have not shown uniform opinions on the etiology, pathogenesis, classification and terminology or treatment of this group of thyroid diseases.

The present report is concerned primarily with a pathologic appraisal of 195 thyroid glands which displayed three types of diffuse thyroiditis, 1) lymphadenoid goiter ("Hashimoto" thyroiditis, struma lymphomatosa), 2) granulomatous or giant-cell thyroiditis, and 3) "Riedel" thyroiditis (Table 1). Included in this study were an additional 159 glands in which

TABLE 1. CHRONIC THYROIDITIS WITHOUT OTHER PATHOLOGIC LESIONS

1. Lymphadenoid type ("Hashimoto")	170
2. Giant-cell or granulomatous type	23
3. "Riedel" type	2
Total cases	195

the chronic thyroiditis of the "Hashimoto" type was either focal or was associated with other diseases of the thyroid gland (Table 2).

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** Deceased.

The purposes of this paper are 1) to describe and illustrate the pathologic lesions of each of the three types of chronic thyroiditis, 2) to make clinical correlations which may aid in the clinical diagnosis, 3) to delineate and emphasize the wide scope of the pathologic manifestations of lymphadenoid goiter, 4) to clarify the interrelationships of lymphadenoid goiter with hyperplastic, involutionary and neoplastic processes in the thyroid gland, and 5) to discuss various views regarding the etiology and pathogenesis of each type of chronic thyroiditis.

TABLE 2. CHRONIC THYROIDITIS—LYMPHADENOID ("HASHIMOTO") TYPE—FOCAL, OR ASSOCIATED WITH OTHER PATHOLOGIC THYROID LESIONS

1. Focal thyroiditis		17
2. Hyperplasia with focal thyroiditis		8
3. Hyperplasia with thyroiditis		42
4. Involutionary nodules with focal thyroiditis		18
5. Involutionary nodules with thyroiditis		28
6. Neoplasm with thyroiditis		46
a) Adenoma with focal thyroiditis	3	
b) Adenoma with thyroiditis	6	
c) Carcinoma with focal thyroiditis	11	
d) Carcinoma with thyroiditis	24	
e) Lymphosarcoma with thyroiditis	2	
Total cases		159

METHODS OF STUDY

This study was limited to patients who had had degenerative and inflammatory disease of the thyroid gland of nonspecific or unknown etiology. The majority of patients were seen by members of the Thyroid Clinic of the University of California Hospital. All patients underwent either subtotal thyroidectomy or thyroid biopsy. A few patients on whom autopsies had been performed in other hospitals were included in the study because the clinical records and pathologic lesions presented instructive features.

The investigation included first a detailed review of the gross and microscopic features of the surgically removed thyroid glands. From the histologic characteristics, a pathologic classification of chronic thyroiditis was derived (Tables 1 and 2).

The clinical records of the majority of patients were available for study; the clinical data were reviewed and correlations made subsequent to the pathologic study.

DEFINITION OF THE THREE TYPES OF CHRONIC THYROIDITIS

Lymphadenoid goiter ("Hashimoto" thyroiditis, struma lymphomatosa).

This type of chronic thyroiditis is characterized by epithelial degeneration followed by follicular regeneration and reorganization, associated with varying degrees of lymphoid infiltration and fibrosis. The pathologic picture first described by Hashimoto (4) represents only one phase or variant of the disease. This lesion may progress to an extensive fibrous replacement of the thyroid gland.

Granulomatous or giant-cell thyroiditis. This process consists of acute necrosis of thyroid follicular epithelium associated with acute and chronic inflammation, followed by fibrosis and follicular regeneration and reorganization. This disease has been described previously by DeQuervain and Giordanengo (25), Crile (17) and others (26).

"Riedel" thyroiditis. In this study there were but two thyroid glands characterized by pronounced fibrous invasion of the adjacent cervical tissues, a feature described prominently by Riedel (1, 2, 3). For purposes of classification we have regarded these two glands in our study as examples of "Riedel" thyroiditis.

INCIDENCE OF CHRONIC THYROIDITIS

From January 1920 to January 1950 a total of 6,571 thyroidectomies were performed at the University of California Hospital. There were 195 patients who had chronic thyroiditis of the three types shown in Table 1. The incidence of chronic thyroiditis among patients requiring thyroid surgery at this hospital during the thirty-year period was therefore 2.9 per cent. There was no significant change in the incidence during each of the last three decades.

RESULTS AND CONCLUSIONS

I. Lymphadenoid goiter ("Hashimoto" thyroiditis, struma lymphomatosa)

Pathologic lesions

Gross examination. Of the 170 thyroid glands in this group, complete surgical and pathologic records, including weights of glands, were available for study in 168 cases. The glands varied widely in size, weight, color and consistency. The pathologic data are summarized in Table 3. The weights of the surgically removed thyroid tissue covered a wide range (Fig. 1). In most cases the thyroid enlargement was diffuse and symmetrical, so that the gland tended to retain the normal thyroid form. When the enlargement was asymmetrical, the right lobe was usually larger. The pyramidal lobe was enlarged in several patients. Seven of the 168 glands extended retrotracheally. Two almost completely encircled the trachea, causing tracheal compression in one instance and extending bilaterally to the cervical spine in the other. Two other thyroid glands caused tracheal constriction, relieved by resection of the isthmus in one patient and causing fatal respiratory obstruction in the other. All 4 of the constricting glands were of the dense fibrous type.

In 37 of the 168 patients (22 per cent), the thyroid gland was adherent in some degree

to surrounding cervical structures, including muscles and trachea. The adherent muscles occasionally were fibrous. The adherent glands were generally those having a fibrotic parenchyma, but many fibrous glands were not adherent. Even when fibrous adherence was pronounced, the glandular capsules remained distinct.

The surfaces of 20 per cent of the thyroid glands were mildly granular, coarsely lobulated, or even presented gross nodularity. When sectioned, the majority of glands showed diffuse alteration by the disease process, although in some instances it was limited

TABLE 3. PATHOLOGIC DATA

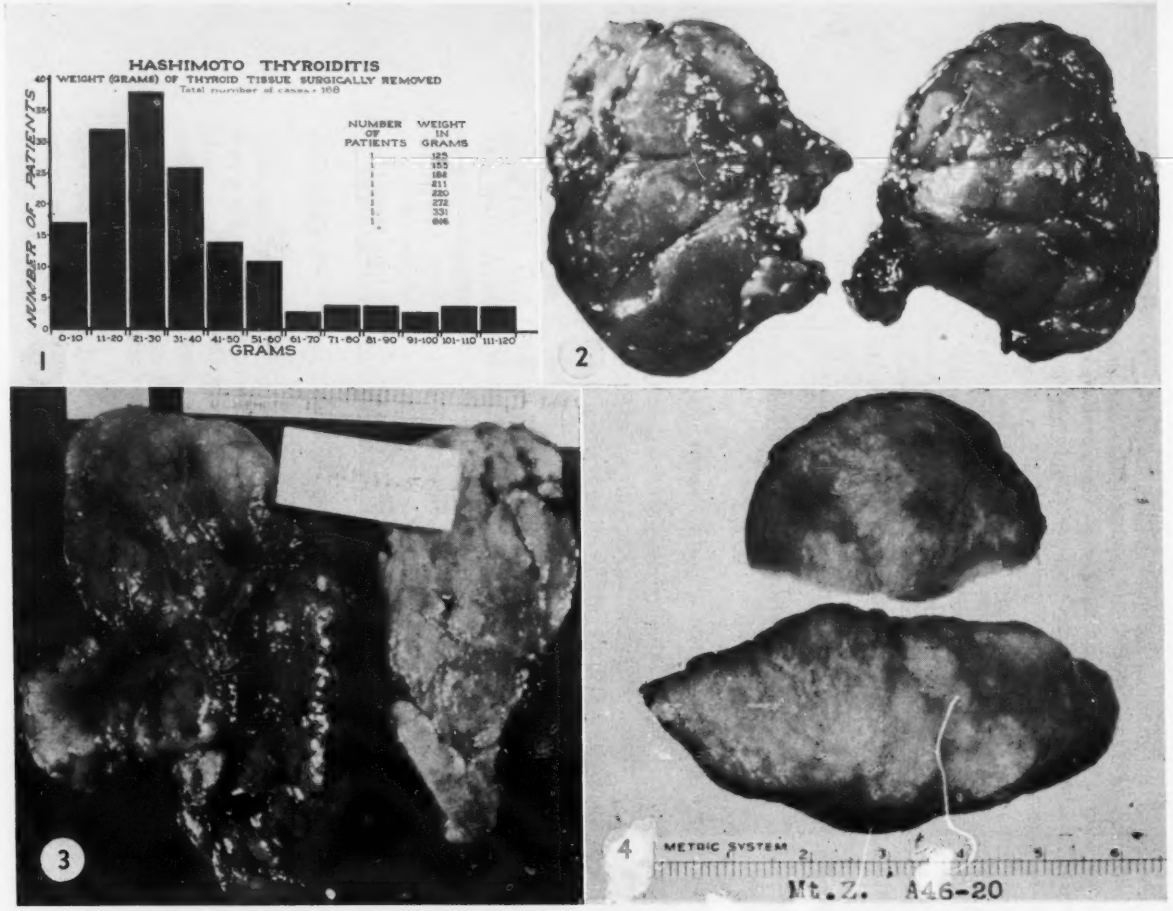
Thyroid	Hashimoto (170 cases)	Granulomatous (23 cases)	Riedel (2 cases)
Weight	10–211 Gm. (mean—39.3 Gm.)	8.5–74 Gm. (mean—25.2 Gm.)	38 Gm. & 55 Gm.
Symmetry	92% symmetrical	84% asymmetrical	Asymmetrical in both cases.
Adherence	22% adherent	57% adherent	Adherent in both cases.
Surface:			
lobulated or nodular	20%	Normal	Infiltrating surrounding tissues.
Color:			
red	7%	39%	
yellow or yellow-pink	81%	44%	
white or grey	12%	17%	
Consistency:			
soft and friable	26%	11%	Outer layers dense, white and fibrous.
rubbery	10%		
firm	35%		Inner portions soft, friable and degenerating.
hard	16%	89%	
dense or woody	12%		
Nodules (within gland)	27%	33%	In both cases.

to one lobe or to segments of one or both lobes. The altered portions of a gland often varied in color and consistency from each other.

The color of the thyroid tissue was most often yellow or yellowish-pink, and these glands were as a rule firm and rubbery (Figs. 2 and 3). Twelve per cent of the glands were glistening, white or greyish-white, and hard or fibrous in consistency (Fig. 4). Only 7 per cent in this group were darker, more vascular and composed of soft friable tissues. Diminished or absent colloid was generally noted.

In the softer or moderately firm glands, fibrous widening of interlobular septums was a prominent feature, and this process often isolated rounded or nodular and pink or yellow masses of thyroid parenchyma. Well circumscribed, small nodules were observed in 45 of the glands (27 per cent). Multiple colloid cysts were seen in several of the largest glands. The harder fibrotic glands had a homogeneous parenchyma, and nodularity of the tissue was not apparent (Fig. 4).

Microscopic examination. Among the 170 glands in this group there were extreme cytologic and histologic variations. The majority showed diffuse alteration by a uniform



Lymphadenoid goiter ("Hashimoto" thyroiditis)

FIG. 1. Chart showing weights of surgically removed thyroid tissue.

FIG. 2. *Early stage.* The tissue is firm, lobulated and yellowish-pink. Little colloid is visible.

FIG. 3. *Later stage.* The tissue is firmer but resilient and pale pink.

FIG. 4. *Late stage.* Shown are horizontal sections of each lobe. The tissue is greyish-white, fibrous and extremely hard.

pathologic process; in some glands there was incomplete involvement by the disease. Judged by microscopic appearances, the stage of the disease process often varied in different segments of the same gland. Alteration of the epithelial, lymphoid and fibrous elements appeared to vary in their rates of progression. The stage of the disease in the 170 glands was classified as "early" in 80 cases, "intermediate" in 68 cases and "late" in 22 cases. This classification was based upon the extent of replacement of the epithelium by either lymphoid or fibrous tissue or both. In this series of 170 glands, transitional stages between lymphoid and fibrotic glands were observed frequently.

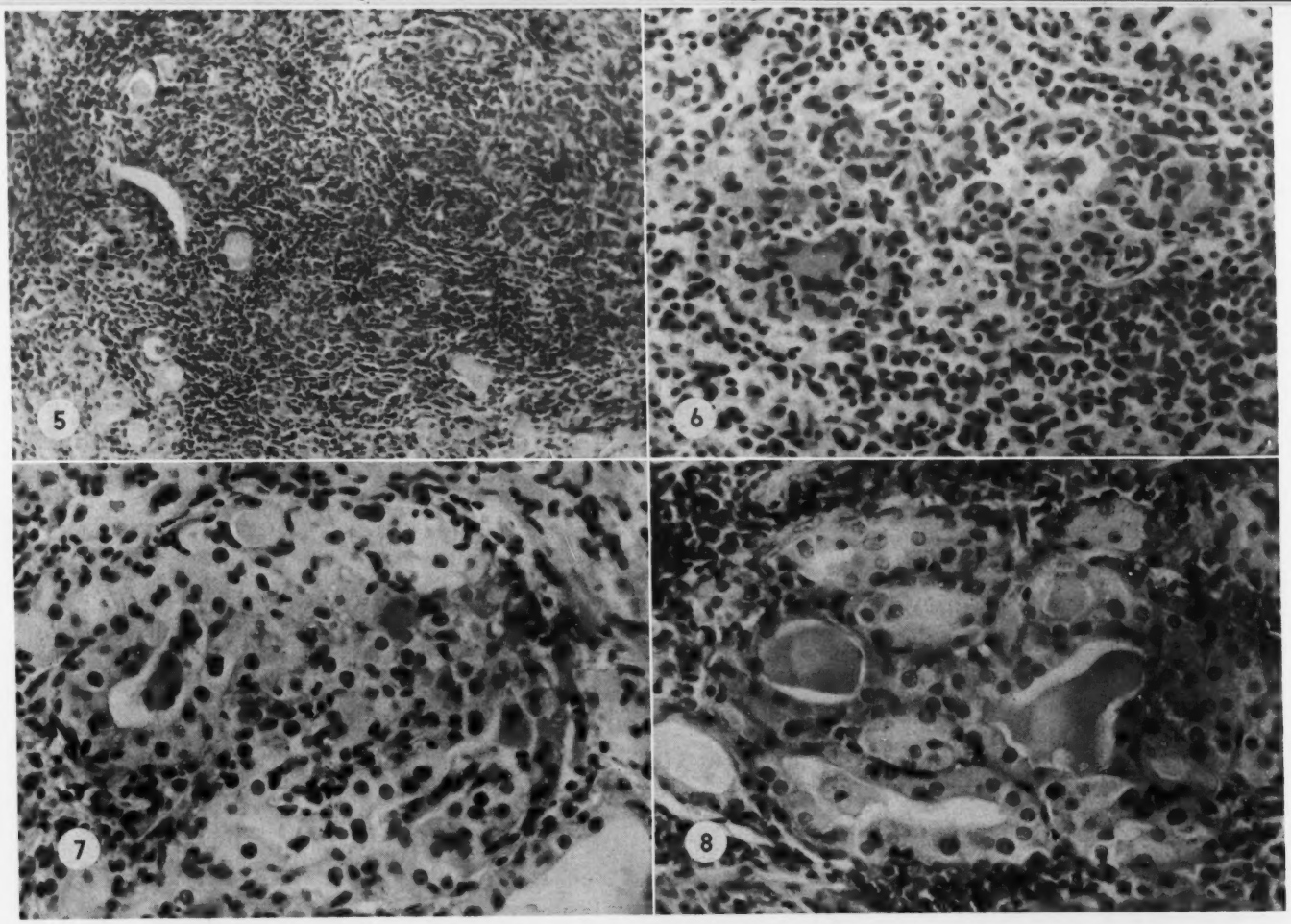
The basic and earliest lesion in this form of thyroiditis appears to be a degenerative change of the thyroid epithelium. At this stage the thyroid epithelial cells correspond to the classic description of Askanazy (27) and are characterized by nuclear pleomorphism and usually by an abundance of eosinophilic or vacuolated cytoplasm. The thyroid follicles appear disrupted, and the thyroid epithelial cells lie in small, irregular groups (Fig. 5). At this stage the fibrous tissue is not proliferating, but the supporting stroma is mildly and diffusely infiltrated with lymphocytes. In later stages the thyroid epithelial cells become smaller and regain a normal appearance. The excessive cytoplasmic eosinophilia disappears. The thyroid epithelium then proliferates and, accompanied by a supporting connective tissue stroma, gradually refills the pre-existing thyroid follicular spaces (Fig. 6). In this early proliferative stage mitotic figures are numerous. Gradually the proliferating epithelium forms small rounded masses, each with a distinct envelope of delicate connective tissue. Syncytial groups of epithelial cells are occasionally observed at this stage (Fig. 6). Lymphoid infiltration is still diffuse and minimal. Still later the groups of thyroid cells assume a follicular pattern (Fig. 7) and some colloid appears in the follicular lumens (Fig. 8). In still later stages the thyroid follicles may reach the size of normal ones and, judging from the appearance of the thyroid epithelial cells and the abundance of colloid, presumably are capable of functioning.

In many glands these larger follicles are hyperplastic or may even store excessive amounts of colloid. The general pattern of this hyperplastic tissue arising from re-formed thyroid follicles is easily distinguished from hyperplastic thyroid tissue in which the basic lesions of thyroiditis of this type appear to be secondary. Even in glands in which re-formation of small thyroid follicles is extensive, lymphoid infiltration may remain minimal. In many instances, especially when mononuclear infiltration is diffuse, many of the cells are plasma cells. At one stage of the disease the majority of small follicles may contain syncytial masses of epithelial cells in their lumens, in which colloid is usually absent (Fig. 9). Often these groups of cells within the lumens appear as small polyps, since they show continuity with the thyroid epithelial cells lining the follicles. The cells comprising these syncytial groups closely resemble the adjacent follicular cells rather than macrophages (28, 29). Evidences of ingestion of colloid by these cells were not observed.

The fibrous proliferation appears to arise in conjunction with the early epithelial proliferation. The connective tissue serves as a supporting framework for the regenerating epithelial cells and carries with it a delicate vascular supply. As the fibrous tissue becomes more abundant in some glands, it assumes a keloid-like pattern characterized by formation of broad, branching bands of hyalinized connective tissue (Fig. 10). In some glands extensive areas of fibrous replacement of parenchyma lie immediately adjacent to lymphoid zones possessing numerous lymphoid follicles (Fig. 11).

The lymphoid component of the disease is scanty in the earlier stages; later there may be an extreme abundance of lymphoid tissue, often with numerous distinct lymphoid follicles with germinal centers (Fig. 12). Among the 170 glands, those demonstrating this classic lymphoid replacement were in the minority. Generally associated with an abun-

FIG. 4. *Late stage.* Shown are horizontal sections of each lobe. The tissue is greyish-white, fibrous and extremely hard.



Lymphadenoid goiter ("Hashimoto" thyroiditis) ×160.)

FIG. 5. Disorganization of thyroid epithelium, evidences of cellular exhaustion and early lymphoid infiltration. (Hematoxylin and eosin,

FIG. 6. Intrafollicular proliferation of epithelium. Note syncytial group of epithelial cells. (Hematoxylin and eosin, ×320.)

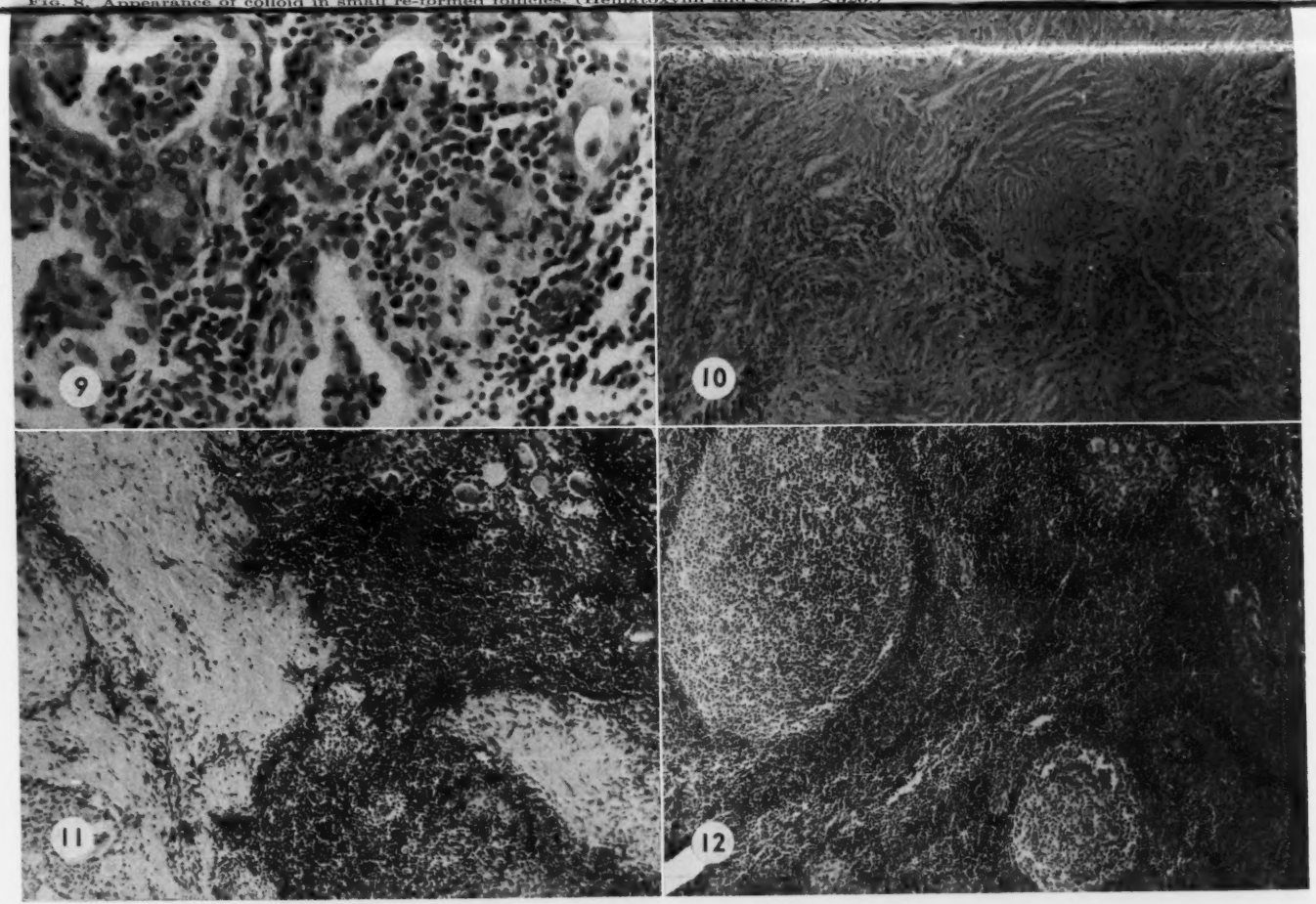
FIG. 7. Differentiation of small follicles. (Hematoxylin and eosin, ×320.)

FIG. 8. Appearance of colloid in small re-formed follicles. (Hematoxylin and eosin, ×320.)

FIG. 6. Intrafollicular proliferation of epithelium. Note syncytial group of epithelial cells. (Hematoxylin and eosin, ×320.)

FIG. 7. Differentiation of small follicles. (Hematoxylin and eosin, ×320.)

FIG. 8. Appearance of colloid in small re-formed follicles. (Hematoxylin and eosin, ×320.)



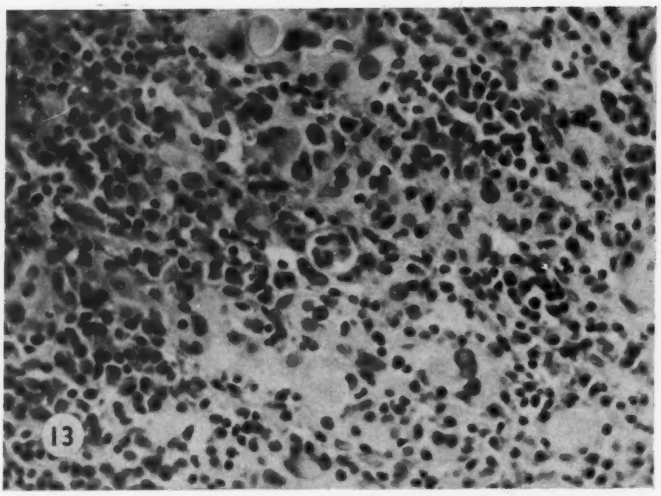
Lymphadenoid goiter ("Hashimoto" thyroiditis)

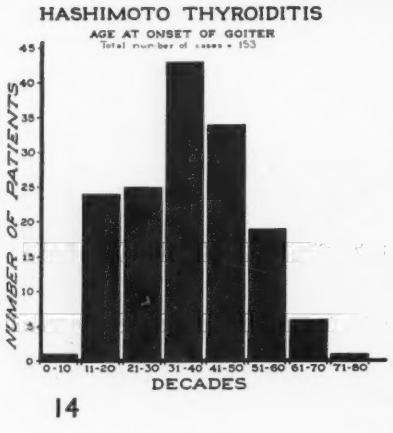
FIG. 9. Syncytial groups of intrafollicular epithelial cells. (Hematoxylin and eosin, ×320.)

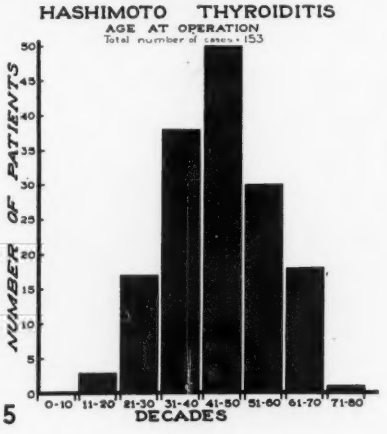
FIG. 10. *Late stage.* Photomicrograph of gland shown in Figure 4. Extensive hyaline fibrosis, moderate lymphoid infiltration and few residual groups of atrophic epithelial cells. (Hematoxylin and eosin, ×80.)

FIG. 11. Pronounced fibrosis immediately adjacent to lymphoid zone. (Hematoxylin and eosin, ×80.)

FIG. 12. Classic pattern of "Hashimoto" thyroiditis, showing abundant lymphoid tissue with large lymphoid follicles. (Hematoxylin and eosin, ×80.)




HASHIMOTO THYROIDITIS
AGE AT ONSET OF GOITER
Total number of cases = 153
NUMBER OF PATIENTS
0 5 10 15 20 25 30 35 40 45
0-10 11-20 21-30 31-40 41-50 51-60 61-70 71-80
DECADES
14


HASHIMOTO THYROIDITIS
AGE AT OPERATION
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NUMBER OF PATIENTS
0 5 10 15 20 25 30 35 40 45 50
0-10 11-20 21-30 31-40 41-50 51-60 61-70 71-80
DECADES
15

Lymphadenoid goiter ("Hashimoto" thyroiditis)

FIG. 13. Epithelial cellular changes of exhaustion in later stages. (Hematoxylin and eosin, ×320.)

FIG. 14. Chart showing age of patients at onset of goiter.

FIG. 15. Chart showing age of patients at time of thyroidectomy.

dance of lymphoid tissue were further evidences of thyroid epithelial degeneration, characterized by nuclear pleomorphism and cellular eosinophilia associated with the loss of colloid (Fig. 13). These epithelial changes are not invariably present in glands showing thyroiditis of this type. However, they may appear at any stage of the disease and are not necessarily associated with excessive lymphoid infiltration.

In some fibrotic glands, squamous metaplasia of portions of the residual epithelium

was observed. Fibrous thickening of the vascular walls with narrowing of the lumens is often found in the few remaining blood vessels in the fibrotic glands. Extensions of fibrous and lymphoid tissue from the capsule into the perithyroid tissues were often seen in glands showing moderate or severe degrees of fibrosis.

Clinical data

The ages of the patients at the time of the appearance of the goiter and at the time of operation showed wide variations (Table 4 and Figs. 14 and 15). The majority of goiters originated, however, during the child-bearing period. Although goiters in general

TABLE 4. CLINICAL DATA

	Hashimoto (170 cases)	Granulomatous (23 cases)	Riedel (2 cases)
Age (at operation)	Range: 17–73 yrs. mean: 31.7 yrs.	Range: 23–63 yrs. mean: 42.6 yrs.	24 & 57 yrs.
Sex	99% female	83% female	Both female
Endemic residence	49%	48%	0
Duration of goiter	40%—1 yr. or less (range, 1 mo.–30 yrs.)	83%—less than 4 mos.	5 mos.; and 2 yrs.
Growth of goiter	48%	39%	In both cases
Symptoms prior to goiter (fever, malaise, etc.)	0	43%	0
Pressure effects	98%	52%	In both cases
Pain or tenderness	15%	52%	In 1 of the 2 cases
Hyperthyroidism	12%	13%	0
Hypothyroidism	2%	4%	0
Correct preop. diagnosis	21%	52%	0

are much more common in females, no other type of thyroid disease demonstrates the peculiar sex incidence of "Hashimoto" thyroiditis—its most striking clinical feature. A history of residence in an endemic area was obtained with essentially the same frequency as in the general outpatient population. Continued growth of the goiter had occurred in half of the patients, a fact which would be of scant aid in the clinical diagnosis. Although various authors have felt that systemic complaints may be associated with "Hashimoto" thyroiditis, this has not been our experience, save in the few instances in which hyperthyroidism or hypothyroidism was also present. Prodromal symptoms have not been identified in this disease. As might be inferred from the fact that all our patients were operated upon, nearly all had local pressure symptoms, most commonly, dysphagia. Pain and tenderness in the thyroid gland were uncommon complaints.

With the variations in the clinical picture of "Hashimoto" thyroiditis the correct preoperative diagnosis was made in only one fifth of the patients. The indications for thyroidectomy in this group were for relief of pressure symptoms or suspicion of a neoplasm, especially if the goiter was of recent origin and had steadily grown. Postoperative hypothyroidism occurred in fully one third of our cases, an incidence distinctly greater than that in this clinic for involutionary nodular goiters (18 per cent).

Comment

Our studies have indicated that chronic thyroiditis of this type has a wider spectrum than that described by Hashimoto (4) and is not limited to the picture of lymphadenoid goiter. The disease may be focal in its distribution; it may be more extensive but not entirely diffuse; or, finally, the entire gland may be involved by the disease. Although lymphoid infiltration and fibrosis often appear to predominate in the pathologic lesion, the primary alteration occurs in the epithelium. The earliest changes characterized by nuclear hyperchromatism and pleomorphism and increased eosinophilia of the epithelial cytoplasm have generally been considered to be those of cellular exhaustion (30). Our studies suggest that in Graves' disease this exhaustion may follow prolonged stimulation by thyrotropic hormone. In a recent careful study Levitt (31) has demonstrated progressive epithelial, lymphoid and fibrous changes following thyroid hyperplasia associated with hyperthyroidism. In our patients a comparatively small number had clinical or laboratory evidences of hyperthyroidism. It seems likely that in the majority of instances the epithelial exhaustion follows thyroid hyperplasia unassociated with excessive production of thyroid hormone. In other words, the hyperplasia leading to epithelial exhaustion in this disease may be the result of an absolute or relative deficiency of iodine.

Although exhausted functionally, the thyroid epithelium appears to be capable of considerable regenerative activity. This proliferative stage of lymphadenoid goiter has been stressed by Williamson and Pearse (6). It seems likely that repeated cycles of exhaustion, regeneration and return of function occur in this long-standing disease. The administration of desiccated thyroid may cause regression of the goiter of "Hashimoto" thyroiditis (24) by reducing the demand on the thyroid epithelium for regeneration and further functional activity. The frequency of the appearance of the basic lesions of "Hashimoto" thyroiditis in involuting hyperplastic glands and in glands also containing nodules of involutionary origin, suggests an involutionary origin for both processes. The concept of follicular versus cellular involution has been proposed previously by Friedman (32).

The fibrous component of the lesion has an insidious beginning. Evidence suggests that it first appears as a supporting framework for the intrafollicular proliferating epithelium. As the disease progresses the fibrous tissue often becomes more abundant and appears as broad hyaline bands separating atrophic fragments of thyroid epithelium. This fibrosis often involves the capsules and leads to some degree of adherence to the surrounding cervical structures. In our cases, however, extensive invasive fibrosis like that described by Riedel (1, 2, 3) did not occur in this type of thyroid disease. Although the primary lesion of the process appears to be

in the epithelium the extensive fibrosis in later stages undoubtedly causes further epithelial degeneration.

The lymphoid infiltration occurring in this disorder varies considerably in its extent. In earlier stages it tends to be minimal and diffuse. When the disease is focal, the lymphoid infiltration is limited to those areas showing the basic epithelial degeneration and regeneration. When present in a diffuse form, plasma cells in large numbers often accompany the infiltrating lymphocytes. The number of glands having very large amounts of lymphoid tissue, usually with lymphoid follicles, is comparatively small. To limit the study of this type of thyroiditis to these particular glands would seem to be an error, since this seems to be but one stage or perhaps one form in which the disease may appear. As the amount of fibrous tissue increases, the lymphoid component decreases. Why progression of the thyroiditis occurs, with fibrosis in some glands and with increasing lymphoid infiltration in others, remains unknown. Since the disease is so variable in its distribution within the gland and in the extent of the fibrous and lymphoid components, judgment as to its progression, based on the results of repeated biopsies, would seem hazardous.

There has been considerable speculation as to the cause of the lymphoid proliferation. Ferguson (33) believes that it is the result of irritation by hydrolyzed lipid materials from colloid. More recently Hellwig (28, 29) has proposed that the lymphoid infiltration results from irritation by colloid, following ingestion of this material within the follicles by macrophages. It has been suggested that, since lymphoid tissue will inactivate thyrotropic hormone (34), presumably this substance will cause proliferation of lymphoid tissue in the thyroid gland (24). In one of our fatal cases (suicide) with a goiter of ten years' duration, there was an extremely large hyperplastic thymus gland and abundant lymphoid tissue in all portions of the body. However, other evidences of excessive thyrotropic activity (exophthalmos and lymphocytosis) were not observed in our patients, except in those with frank hyperthyroidism. We are proposing that the lymphoid infiltration in "Hashimoto" thyroiditis may be comparable to that observed in various tissues being invaded by neoplastic epithelium, since proliferation of the thyroid epithelium in thyroiditis may be pronounced.

It is apparent that the epithelial disease, the lymphoid infiltration and the fibrosis may proceed at variable rates. It also seems likely that the disease is cyclic in its progression. Although not entirely definite, in general it may be stated that the more fibrotic glands are found in older individuals.

The etiology of this type of thyroiditis remains obscure. It has been generally concluded that it is a metabolic rather than an infectious type of thyroid disease. Some years ago McCarrison (35, 36, 37) produced in

the rat a thyroid lesion which bore a remarkable resemblance to the human lesion. This work has not been extended or confirmed. The lesion was produced by a diet deficient in vitamins and manganese. In a large series of various animals fed diets deficient in one or in many vitamins, Rinehart (38) has never observed lesions of the thyroid gland resembling "Hashimoto" thyroiditis.

Since the disease occurs almost exclusively in females, a relationship to the ovarian hormones has been suggested. However, to date, thyroid lesions have not been produced experimentally by excesses or deficiencies of the ovarian hormones. In our series, 168 of the 170 patients with this disease were females, but the wide distribution of ages at the onset of goiter would seem to preclude a direct relationship to ovarian functions. The higher incidence of involutionary nodular goiters in females residing outside of endemic areas has been explained by the greater demands for iodine during menstruation, pregnancy and lactation (30). Thus a relative deficiency of iodine occurring in females may account for the lesion of thyroiditis, as well as for the development of involutionary nodular goiters.

Data concerning family history of goiter, history of residence in an endemic area, number of pregnancies and history of menstrual irregularities, were compiled in our group of patients with "Hashimoto" thyroiditis. These data were contrasted with those from a comparable group of control patients of the same ages and social status, observed during the same period. There were no significant differences as to residence in endemic areas, the number of pregnancies or the incidence of menstrual irregularities in patients with chronic thyroiditis as compared to the control group. There was a significantly increased incidence of family history of goiter in patients with "Hashimoto" thyroiditis as compared to the control group. Our data concerned with family histories of neoplasms, or with nonthyroid neoplasms in the patient, were not considered to be reliable.

The patients included in this study who had typical hyperplasia associated with hyperthyroidism had glands differing from those usually seen in Graves' disease, in that the basic lesions of "Hashimoto" thyroiditis were also present. The cellular changes of exhaustion occasionally seen in Graves' disease and in adolescent goiters due to relative or absolute iodine deficiency closely resemble those of "Hashimoto" thyroiditis. However, in most instances the toxic diffuse and the adolescent goiters do not show the follicular disruption and reorganization seen in chronic thyroiditis, even though lymphoid infiltration and fibrosis may be present. In 2 hyperplastic glands which were examined two months following treatment by I^{131}, typical lesions of Hashimoto's thyroiditis were observed (39). These patients had not had other therapy.

There are some resemblances of the "Hashimoto" gland to those seen in myxedema and adult cretinism. In the latter instances fibrosis, thyroid

epithelial atrophy and lymphoid infiltration may also be observed. However, the proliferative epithelial reaction characteristic of thyroiditis is absent, the inflammatory infiltration is minimal and the fibrous tissue more closely resembles condensed thyroid stroma than it does the proliferating fibrous tissue of thyroiditis. Thyroid glands in patients with pituitary atrophy or degeneration have shown simple atrophy without the characteristic lesions of thyroiditis. In 2 patients with Addison's disease resulting from idiopathic degeneration and necrosis of the adrenal cortex, enlarged thyroid glands demonstrating the typical lesions of chronic thyroiditis have been observed by us. Both glands were characterized by an abundance of lymphoid tissue widely separating atrophic thyroid follicles. For comparison we have studied thyroid glands invaded by lymphoid cells in lymphatic leukemia and in cervical lymphosarcoma. In no instance did it appear that the infiltrating lymphoid tissue had produced atrophic changes in the thyroid epithelium comparable to those seen in "Hashimoto" thyroiditis (39).

II. Granulomatous or giant-cell thyroiditis

Pathologic lesions

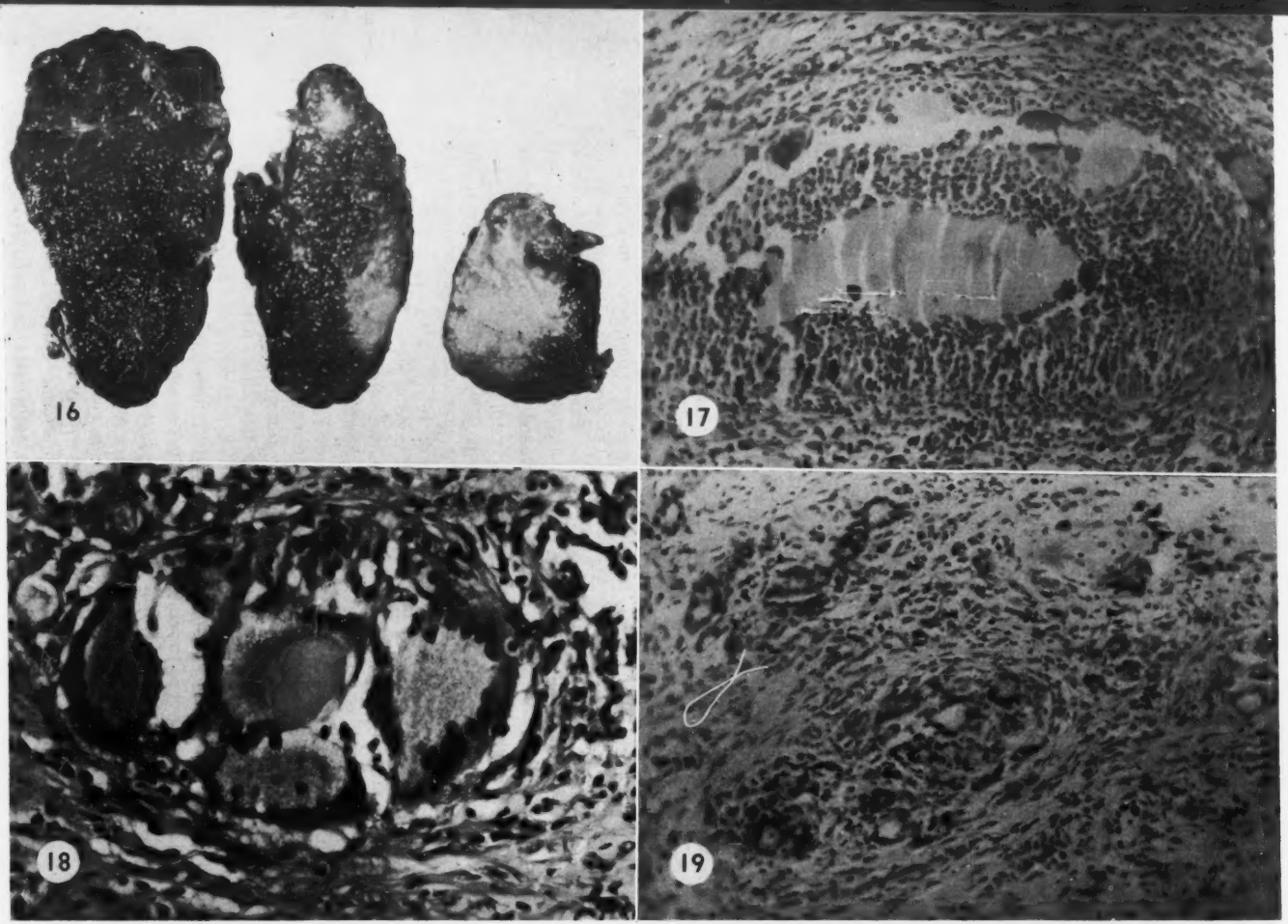
Gross examination. Adequate clinical and pathologic descriptions, including weights of glands, were available in 18 of the 23 cases. The thyroid glands in this group were rarely enlarged. The mean weight was 25.2 Gm., with a range of 8.5 to 74 Gm. Only 9 of the glands weighed 25 Gm. or more. The pathologic data are summarized in Table 3.

All but 3 glands in this group were symmetrical. Thirteen of the 19 glands were extensively adherent to the trachea or adjacent muscles. There was only faint lobulation of the capsular surfaces. These were smooth and hard. Externally no nodules were evident although, when sectioned, 6 of the glands contained small circumscribed nodules. One gland showed retrotracheal extension.

Generally these glands had a pale yellow, white, or greyish-pink parenchyma. The majority showed uniform alteration but, in a few, the character and consistency of the tissue varied in different portions of the two lobes (Fig. 16). With two exceptions these glands were firm, hard, or even of the consistency of wood or stone. The majority were frankly and extensively fibrous throughout or presented numerous interlacing fibrous bands in a more vascular fleshy parenchyma. One hard resilient gland severely constricted the trachea.

Microscopic examination. This type of thyroiditis presents a distinct histologic appearance. The earliest lesion is focal and generally involves small localized groups of thyroid follicles. There is acute degeneration of the follicular epithelium with desquamation of the degenerating cells into the follicular lumens. These degenerative and necrotic cellular changes are accompanied by neutrophilic leukocytic infiltration which involves the perifollicular spaces as well as the epithelial layer. Often an acute inflammatory exudate is observed in the follicular lumens. As the lesion progresses, more of the thyroid parenchyma is involved, and often lesions of varying age and extent are observed in the same thyroid gland. The acute inflammatory reaction subsides and is replaced by a chronic inflammatory cellular infiltration associated with proliferation of perifollicular fibrous tissue. Eosinophilic leukocytes are occasionally found in large numbers.

At this stage the remaining follicular epithelium proliferates and extends into the



Granulomatous or giant-cell thyroiditis

FIG. 16. Several segments of each lobe are replaced by hard, pale yellow tissue. and eosin, ×160.)

FIG. 17. Intrafollicular proliferation of thyroid epithelium. Note the giant cells and residual acute inflammatory exudate. (Hematoxylin

FIG. 18. Numerous giant cells within thyroid follicle. (Hematoxylin and eosin, ×320.) eosin, ×160.)

FIG. 19. *Late stage*, showing re-formation of small follicles, extensive fibrosis and residual chronic inflammation. (Hematoxylin and

follicular spaces (Fig. 17). It is accompanied by a delicate supporting framework of reticulum and fine collagenous fibers. In the earlier stages the epithelium appears as large multinucleated syncytial groups which tend to surround colloid remaining in the lumens (Fig. 18). The nuclear structure of these syncytial giant cells closely resembles that of the thyroid follicular epithelium. However, some syncytial cells found in the follicular lumens in this type of thyroiditis appear to be foreign-body giant cells. Their nuclei are smaller, and more compact and hyperchromatic than those of either the thyroid follicular epithelium or the syncytial epithelial giant cells. In rare instances degeneration and necrosis of the thyroid follicles is followed by extravasation of masses of colloid into the perifollicular tissues.

Later stages of this process are characterized by filling of the pre-existing follicular spaces by solid masses of thyroid epithelial cells enveloped by a connective tissue stroma. By this time considerable perifollicular scarring and chronic inflammatory infiltration are present as well. In the later stages the proliferating epithelium within the follicular spaces then re-forms small thyroid follicles in which colloid may later appear (Fig. 19).

In some glands fibrosis is extensive. The fibrous tissue is cellular, and the collagenous fibers remain delicate and fibrillar. The fibrous tissue seen in this type of thyroiditis does not resemble the broad interlacing hyaline bands characteristic of the fibrotic type of "Hashimoto" thyroiditis. In some instances minimal extension of the proliferating fibrous tissue from the capsule into the adherent muscles was observed. This was accompanied by a moderate degree of lymphoid and plasma-cell infiltration.

Clinical data

The ages of the patients when thyroidectomy was performed covered a wide range, with a mean of 42.6 years (Table 4). All but 4 of the patients were female and a history of residence in endemic areas was obtained in one half of them. The duration of these goiters was brief and, in general, the process did not originate in a thyroid which had previously been enlarged. Over one third of the goiters had continued to grow, but areas of growth were not symmetrical and were directly related to the zones of tenderness. After the onset of the disease these zones of tenderness tended to migrate within the gland. The associated pain occurring in most patients radiated to the angle of the mandible or to the ear. Tenderness in the thyroid gland occurred in 18 patients. Symptoms of pressure were present in half the group, and they were of a most distressing nature. Often there was severe pain on swallowing or turning the head.

In most of the patients prodromal symptoms of fever, malaise or sore throat (apparently due to pharyngitis and not to involvement of the thyroid gland) were present for approximately a week prior to the onset of the local thyroid complaints.

Hypothyroidism is rare in this disease and is related to the gross degeneration of the gland occurring over a period of several months. The clinical data supported the view that thyrotoxicosis was present in 3 patients concurrently with the granulomatous thyroiditis. This opinion seems warranted, even though the systemic effects of the thyroiditis may superficially mimic thyrotoxicosis. In this connection, it should be emphasized that the usefulness of determination of the serum protein-bound iodine is greatly diminished by its frequent elevation in the acute phase of granulomatous thyroiditis.

If the patient is seen during the initial stages of granulomatous thyroiditis, a correct preoperative diagnosis can usually be made. Errors in diagnosis will be greater when the physician is confronted with the hard fibrotic gland found in later stages of the disease.

Spontaneous regression of the symptoms of granulomatous thyroiditis often ultimately occurs, and the speed of this regression may be enhanced by various types of treatment. However, since our patients were subjected to thyroidectomy because of

FIG. 18. Numerous giant cells within thyroid follicle. (Hematoxylin and eosin, ×320.)
FIG. 19. *Late stage*, showing re-formation of small follicles, extensive fibrosis and residual chronic inflammation. (Hematoxylin and eosin, ×160.)

persistent pain in the thyroid or because of pressure symptoms, no comments regarding this aspect can be made.

Comment

Granulomatous or giant-cell thyroiditis is a distinct type of thyroid disease. The frequency of fever and malaise preceding the onset of thyroid symptoms, and the finding in early lesions of acute destruction of thyroid epithelium associated with a leukocytic exudate, suggest that the etiology may be infectious or possibly the result of a sensitizing type of injury.

Regeneration of the thyroid epithelium, leading to the formation of small follicles, is similar in many respects to the proliferative stage of "Hashimoto" thyroiditis. However, the appearance of numerous syncytial giant cells, both of epithelial and foreign body type, is a distinctive feature of this disease. Chronic inflammation, often with considerable fibrosis, may produce a diffusely hard, adherent thyroid gland. This condition undoubtedly has been classified frequently as Riedel's struma by many observers, but DeQuervain and Giordanengo (25) have clearly separated it from other forms of chronic thyroiditis.

III. "Riedel" thyroiditis

Pathologic lesions

Gross examination. Each of the 2 goiters was a hard, unilateral mass, occupying the lower part of one lobe. The pathologic data are summarized in Table 3. In one patient the mass was on the right and in the other, on the left. Both goiters were removed en bloc; one weighed 38 Gm. and the other 55 Gm.

Each mass was not only poorly circumscribed but had actually infiltrated the adjacent sternomastoid muscle. One was fixed to the trachea, with very indefinite lines of cleavage.

The peripheral portion of each mass consisted of dense, gritty, white fibrous tissue which had a concentrically layered appearance. The central portion of each consisted of degenerating, friable tissue which had the appearance of an involutionary nodule (Fig. 20). In one case the nodule was cystic and contained degenerating blood and colloid.

Microscopic examination. Both glands had a similar pattern. The central portion of each consisted of multiple involutionary nodules, composed mainly of enlarged colloid-filled follicles. The peripheral portion of each mass was formed by dense bands of hyaline fibrous tissue infiltrated by numerous lymphocytes and plasma cells and by fewer neutrophilic and eosinophilic leukocytes. Many of the connective tissue cells were immature proliferating fibroblasts. At the margins of the central nodules, the thyroid tissue was being invaded and replaced by the inflammatory connective tissue. Thus, small irregular follicles and nonfollicular groups of thyroid epithelial cells were isolated by the fibrous tissue. Peripherally the chronic inflammatory fibrous tissue was invading striated muscle and causing degeneration and isolation of muscle fibers (Fig. 21).

Clinical data

Only 2 patients, both females, were considered to have "Riedel" thyroiditis. Slow growth of the goiter had occurred over a considerable period and was associated with

"Riedel" thyroiditis

FIG. 20. Degenerating colloid-filled nodule, surrounded by concentric layers of fibrous tissue.

FIG. 21. Photomicrograph of outer layer of fibrous tissue shown in Figure 20. Note invasion of striated muscle by chronic inflammatory fibrous tissue. (Hematoxylin and eosin, ×160.)

distinct pressure symptoms. Thyroid function was considered normal in both instances.

The thyroid gland in each case was unilaterally enlarged, hard, and fixed to the adjacent muscles and trachea. These features led to a preoperative diagnosis of an involutionary goiter in one patient and of carcinoma in the other. The distressing pressure symptoms and the clinical confusion with a malignant neoplasm demanded surgical therapy.

Comment

In our series only these 2 patients had thyroid lesions characterized by actual extensive fibrous invasion of the adjacent cervical tissues. Although there may be considerable glandular adherence in the "Hashimoto" and granulomatous types of disease, the invasive nature of the periglandular fibrous tissue is lacking. Riedel's original descriptions (1, 2, 3) stressed the invasiveness as well as the extreme hardness of the gland.

Our concept of this process is similar to that of Crile (17) who has commented upon the presence of degenerating adenomas in the center of these fibrosed glands. Identical degenerating nodules surrounded by a dense invasive scar have been illustrated by Joll (12) and by Schilling (15) as examples of thyroiditis. Since the proliferating fibrous tissue is heavily infiltrated with chronic inflammatory cells, the process may represent an accentuation of the same lesion described by Plummer and Broders (40) as capsulitis, an inflammatory process in the capsule surrounding degenerating adenomatous nodules. This diseased fibrous tissue has certain resemblances to a keloid scar.

IV. Chronic thyroiditis—"Hashimoto" type—focal, or associated with other thyroid lesions

Included in this study were an additional 159 patients who had various forms of thyroid disease (Table 2). In addition, gross and microscopic examination of their thyroids showed these glands also to be the site of chronic thyroiditis of the "Hashimoto" type. In most instances the thyroid had been removed because of thyrotoxicosis or nodular goiter. In some instances a clinically evident neoplasm was the reason for thyroidectomy.

The majority of these glands were enlarged. Approximately 25 per cent were adherent in some degree to surrounding structures. Gross examination usually revealed the major pathologic lesion, as well as gross evidences of chronic thyroiditis. For example, the hyperplastic glands had a typical red, vascular, meaty appearance but, in addition, showed areas of lymphoid infiltration and fibrosis. Likewise, those glands containing nodules of involutionary origin had the typical gross appearance of such nodular goiters (41, 42). The glands containing benign and malignant neoplasms also showed gross evidences of chronic thyroiditis.

The process classified as focal thyroiditis of the "Hashimoto" type (Table 2) appears to represent an early stage of the more diffuse process. Actually, there is no significant difference between this focal thyroiditis and the slightly more extensive disease classified in the "Hashimoto" group included in Table 1. Joll (12) was unwilling to include the focal lesion under the heading of thyroiditis, since he believed it occurred in thyrotoxic goiters, in the thyroid gland of myxedema and in the glands of

involutional and unclassified chronic inflammatory states. This focal lesion differs, however, from the common localized lymphoid infiltrations of the thyroid, in that it is characterized by distinct focal epithelial disease as well.

Regardless of the type of accompanying disease, the pattern of the localized or diffuse chronic thyroiditis was identical with that already described. Follicular disruption, epithelial proliferation, lymphoid and plasma-cell infiltration and fibrosis occurring in these glands were identical with the lesions found in glands without other accompanying thyroid disease. Furthermore, the degenerative and inflammatory reactions of thyroiditis occurred in portions of the glands in which evidences of other diseases were not present. It was, therefore, concluded that these changes were not the result of pressure by enlarging nodules and did not represent a reaction to invasion by a malignant neoplasm.

Microscopic examination of glands in this group showed the typical patterns of hyperplasia with varying degrees of involution, of involutionary nodules in various stages of development, or of benign or malignant neoplasms (most of which were of epithelial origin).

The relation between chronic thyroiditis of the "Hashimoto" type and benign or malignant neoplasms of the thyroid gland is of considerable interest. We have noted a significant difference between the incidence of malignant thyroid neoplasms in glands with "Hashimoto" thyroiditis and in glands free of this inflammatory and degenerative lesion. At the University of California Hospital, 191 malignant thyroid neoplasms have been found in 6,367 thyroid glands free of thyroiditis of the "Hashimoto" type, an incidence of 3 per cent. Thirty-seven malignant neoplasms have been observed in 302 glands also showing "Hashimoto" thyroiditis, an incidence of 12 per cent. With the population involved, the difference between these two percentages is significant at the 0.1 per cent level; that is, it would occur by chance less than one time in one thousand.

In those glands containing benign or malignant neoplasms, the accompanying thyroiditis was localized in 14 cases and was diffuse in 32 cases. In several glands showing both processes, epithelium which was transitional between the proliferating epithelium of typical "Hashimoto" thyroiditis and malignant invasive epithelium was observed. One of these glands has been illustrated previously (43). Four of the 9 adenomas in this group were composed of so-called "Hürthle cells" (44, 45). It is of interest in this connection that, in rats, residual exhausted thyroid cells in glands largely destroyed by I^{131} (46) presumably were the source of malignant, metastasizing thyroid neoplasms (47, 48).

Lymphosarcoma occurred in 2 patients in this group. The relation between lymphadenoid goiter and thyroid lymphosarcoma has been discussed by Graham (49) and by Kellett and Sutherland (50). Review of a

thyroid sarcoma containing giant cells, reported on by Rather (51), has also shown that the thyroid gland was involved by chronic thyroiditis of the "Hashimoto" type.

The clinical diagnosis of "Hashimoto" thyroiditis associated with other diseases in the gland will remain relatively impossible. The reason is clear. The dominant condition, whether an involutionary, neoplastic or toxic goiter, will usually mask any evidences of thyroiditis. Therefore, even though our conception of the spectrum of "Hashimoto" thyroiditis demands inclusion of these cases in a discussion of chronic thyroiditis, it must remain on an entirely nonclinical basis. It is noteworthy, however, that no instances of granulomatous thyroiditis associated with other types of thyroid disease have been encountered.

SUMMARY

A clinical and pathologic study of 195 patients who had had chronic thyroiditis of unknown etiology revealed three distinct types of thyroid disease: 1) lymphadenoid goiter ("Hashimoto" thyroiditis, struma lymphomatosa), 2) granulomatous or giant-cell thyroiditis, and 3) "Riedel" thyroiditis.

Lymphadenoid goiter has a wider pathologic spectrum than is generally appreciated. Proliferative and fibrotic as well as degenerative phases of the disease occur.

This study also included 159 glands in which the basic pathologic patterns of lymphadenoid goiter were focal or were accompanied by hyperplasia, involutionary nodules, or benign or malignant neoplasms. It was concluded that these thyroid diseases have a close relationship to thyroiditis of the "Hashimoto" type. There is a significantly greater incidence of malignant thyroid neoplasms in glands with this type of thyroiditis than in those free of the inflammatory disease.

Each of the three types of chronic thyroiditis may display hard, fibrous thyroid glands, adherent to adjacent structures. The type classified as "Riedel" thyroiditis is the only one characterized by invasive adherence of the gland to surrounding tissues.

Acknowledgment

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LETTER TO THE EDITOR

AN EFFECT OF COMMERCIAL PREPARATIONS OF CORTICOTROPIN UPON THE WORK PERFORMANCE OF THE ADRENALECTOMIZED-HYPOPHYSECTOMIZED RAT

To the Editor

It is generally believed that the biologic effects of corticotropin are mediated exclusively by the hormones of the adrenal cortex. Jacot and Selye (*Endocrinology* **50**: 254, 1952) have noted certain extra-adrenal morphologic effects of some preparations of corticotropin. We have observed a significant effect of three commercial preparations of corticotropin upon work output of the adrenalectomized-hypophysectomized rat.

Male rats, each weighing 200 Gm., were subjected to stimulation of the gastrocnemius muscle by a previously described technique (Ingle: *Endocrinology* **34**: 191, 1944). All of the hormone preparations were administered by continuous intravenous injection during the test period of forty-eight hours. The following points have been established. 1. The subnormal performance of adrenalectomized rats can be restored to normal by adrenal cortical extract. 2. The subnormal performance of hypophysectomized rats is restored to normal by corticotropin. 3. The performance of hypophysectomized rats is improved but is not restored to normal by adrenal cortical extract. 4. The performance of hypophysectomized rats is restored to normal by adrenal cortical extract plus corticotropin. 5. The performance of adrenalectomized-hypophysectomized rats is improved but is not restored to normal by adrenal cortical extract. 6. The performance of adrenalectomized-hypophysectomized rats is restored to normal by adrenal cortical extract plus corticotropin.

Three commercial preparations of corticotropin have been used. When tested in adrenalectomized-hypophysectomized rats given an optimal intake of adrenal cortical extract, the administration of 2 U.S.P. units of Upjohn's corticotropin per rat per day caused an average enhancement of 34 per cent in total work, which brought the work output of these rats up to the level in normal rats. The use of similar doses of Wilson's corticotropin and of Armour's corticotropin (ACTHAR) yielded similar results.

Three possible explanations for the extra-adrenal effects of these samples of corticotropin are as follows. 1. The extra-adrenal action may be due to the presence of a known hormone of the pituitary gland other than corticotropin. 2. The extra-adrenal action may be due to the presence of some unknown principle. 3. The biologic effects of pure corticotropin may not be limited to the adrenal cortices.

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The Endocrine Society

THE 1953 ANNUAL MEETING

The Thirty-fifth Annual Meeting of The Endocrine Society will be held in the Hotel Statler, New York, N. Y., on Thursday, Friday, and Saturday, May 28, 29 and 30, 1953.

The Committee on Local Arrangements is Dr. Earl T. Engle, Chairman, with Drs. Rulon W. Rawson and Sidney C. Werner as members of the Committee.

All Scientific Sessions will be held in the Hotel Statler. The rooms in which each session will be held will be announced in the program and on the hotel bulletin board. The Annual Dinner is scheduled for Friday, May 29, at 7:30 P.M., preceded by cocktails at 6:30 P.M.

All members are urged to make hotel reservations immediately inasmuch as the hotels expect to be filled to capacity. Reservations should be made directly with the Hotel Statler, advising time of arrival and departure date. Make your reservations now and avoid disappointment.

Those wishing to present papers, which will be limited to ten minutes, should send FOUR COPIES of the title and abstract to the Vice-President, Dr. Lawson Wilkins, Johns Hopkins Hospital, Baltimore 5, Maryland, not later than FEBRUARY 1, 1953. **It is imperative that the abstracts be informative and complete with results and conclusions in order that they may be of reference value and suitable for printing in the program and Journals of the Society. The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:**

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. References, if used, must be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.
2. The title heading must be arranged as follows:
   Line 1. Title, not to exceed fifteen words.
   Line 2. Author/s. The name of each non-member author collaborating with member-authors is to be followed by the phrase "(by invitation)." Names of non-members who are introduced, *i.e.*, who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *e.g.*, M.D., of each author should be given after his name.
   Line 3. Institution of origin and city in which institution is located.
3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three additional copies.
4. Abstracts should be letter-perfect, since there will be no opportunity for proof reading by authors.

The Endocrine Society

1953 AWARDS AND FELLOWSHIPS

Awards and Fellowships presented by The Endocrine Society carry no obligation by the recipient to the Society or to the donors.

Fellowships

Society Fellowships are designed to assist men or women of exceptional promise in furthering their educational training and advancement toward a scientific career in endocrinology. Fellowships may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend, which will not exceed $5,000, may be divided into two Fellowships in varying amounts, in accordance with the qualifications of the appointee. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. He must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals. He must submit a program of proposed study, indicate one or more institutions where the proposed program will be followed, and submit statements of approval from the investigators with whom he proposes to conduct his research. He must serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis

THE AYERST, McKENNA AND HARRISON FELLOWSHIP

This Fellowship will not be awarded in 1953 in order that it may accumulate toward a $5,000 Fellowship to be awarded in 1954.

THE SCHERING FELLOWSHIP IN ENDOCRINOLOGY

The Schering Fellowship in Endocrinology was established in 1949 and the first recipient was Dr. D. Laurence Wilson in 1950. Dr. John D. Stoekle was chosen as the recipient of the 1951 Fellowship. Inasmuch as he was unable to accept, due to a call to military service, the same Fellowship was reawarded in 1952 to Dr. C. L. Courtright. The 1953 Schering Fellowship will be in the amount of $5,000 and will henceforth be given in the same amount on alternate years.

Awards

THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH AWARD

This Award of $1,000 was established in 1939 by The Squibb Institute for Medical Research and was given first in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. E. A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori; in 1948 to Dr. Fuller Albright; in 1949 to Dr. Herbert M. Evans; in 1950 to Dr. C. N. H. Long; and in 1951 to Dr. J. B. Collip. None was given in 1943. This Award was increased to the amount of $2,500 beginning with the 1952 Award and the recipient was Dr. James H. Means. A special committee of five members of the Society selects the recipient from among investigators in the United States or Canada, on the basis of outstanding contributions to endocrinology.

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishment of an investigator, not more than thirty-five years of age, in the field of clinical or preclinical endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the Award was presented to Dr. E. B. Astwood; in 1945 to Dr. Jane A. Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li; in 1948 to Dr. Carl Heller; in 1949 to Dr. George Sayers; in 1950 to Dr. Oscar M. Hechter; and in 1951 to Dr. Albert Segaloff. Effective in 1952, the Award was increased from $1,200 to $1,800 and the recipient was Dr. Seymour Lieberman. If within twenty-four months of the date of the Award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $2,500.

Nominations

Each member has the privilege of making one nomination for each Fellowship or Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions to, or interest in, endocrinology and by a bibliography of the nominee's most important publications, with reprints if possible. The nominations should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, and returned to him not later than *March 1, 1953*.

The American Goiter Association

1953 ANNUAL MEETING

The 1953 Annual Meeting will be held *May 7, 8 and 9, 1953*, in the Drake Hotel, Chicago, Illinois.

VAN METER PRIZE AWARD FOR 1953

The American Goiter Association again offers the Van Meter Prize Award of three hundred dollars and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association, which will be held in Chicago, Illinois, May 7, 8 and 9, 1953, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double spaced copy in duplicate sent to the Corresponding Secretary, Dr. George C. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colorado, not later than *February 15, 1953*. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual Proceedings of the Association.

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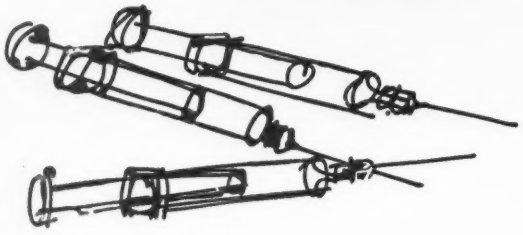

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